ARCHIVES OF DISEASE IN CHILDHOOD

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THE TREATMENT OF RENAL RICKETS

BY

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The condition now called renal rickets was first mentioned by Lucas (1883), and in the next twenty-eight years occasional cases were described. The close association between the kidney and the bony lesions was first clearly pointed out by Morley Fletcher (1911) in a communication to the Children's Section of the Royal Society of Medicine.

Miller (1911), Parsons (1911), Parkes Weber (1912), Naish (1912), and Barber (1913) reported cases in the next year, and since then a large number of cases have been described in England, Canada, the United States and recently in France, Germany and Norway. The important papers by Barber (1920, 1926, 1933) and Parsons (1927), and the reviews by Mitchell (1930), Hamperl and Wallis (1933) give an excellent account of existing knowledge. Although so many papers have been written describing cases, many of which have ended fatally, little has been said about treatment either of the rickets or the kidney lesion. There is a general opinion that neither vitamin D nor ultra-violet light is of any value, and Park (1933) says that ' large amounts of vitamin D may produce calcification in the rachitic intermediate zone, but is useless because the D merely depletes the skeleton at one point in order to affect bone salt deposition at another, and is dangerous because it may lead to injury elsewhere ' (metastatic calcification). György (1928), Duken (1928), Schick (1929) and Karelitz and Kolomayzeff (1932), on the other hand, have each reported a case in which the condition of the bones improved after the administration of vitamin D. Salvesen (1934) found that the clinical condition as regards pain and comfort in walking improved when calcium lactate was given, although it deteriorated when ultra-violet light alone was given. Parsons (1927) and Barber (1926) have each reported one case in which the rickets healed although no vitamin D or ultra-violet light was given.

The kidney lesion is usually a chronic focal nephritis, and is often associated with a congenital lesion. The condition is regarded as unalterable and the treatment is not discussed. The changes which occur in the blood during the course of the disease are important. The observation by Green (1922) than an acidaemia may be present has been confirmed by many observers, and Schoenthal and Burpee (1930) and Salvesen (1934) have tried to correct it. We have treated two patients with sufficient alkalis to correct the acidaemia

and with large doses of vitamins A and D ; the results of this treatment have been striking.

Case records

Case 1, W. L., aged fifteen, was born at term of healthy parents, birth weight 9 lb. after a normal delivery. He was a healthy baby and, with the exception of rubella at the age of seven, never had any infectious fevers, sore throats or other serious illness. There is no family history of renal disease on either side of the family, and the only other child, a girl of twenty-six, is alive and well. The patient appeared normal until the age of four, when he ceased growing at the usual rate. For the next eleven years, although well, attending school and playing games, he grew slowly. In 1932, when fifteen, he first began to complain of pain in both knees and later also in ankles, heels and wrists, the joints being described as ' swollen and very painful.' This condition persisted for several months, during which the pain in the legs made walking difficult, and in April, 1933, the boy was brought to the Orthopaedic Department af St. Bartholomew's Hospital. He never complained of any thirst.

ON EXAMINATION he was of average mentality, but sallow and undersized, his height being only 51 inches and weight 65 lb., which is 11 inches and 38 lb. below the average for his age. The forehead was high and prominent and the teeth were well formed and in good condition ; the mucous membranes were not pale and his tongue was clean and moist. The chest was barrel-shaped with a wide sub-costal angle and prominent costo-chondral junctions, and the lungs were emphysematous. The cardio-vascular system appeared to be normal ; the retinal vessels were healthy ; the heart was not enlarged and the blood pressure was 108 mm. Hg. systolic and 84 diastolic. The abdomen was slightly protuberant but otherwise natural, neither kidney being palpable. The distal ulnar, radial and the proximal tibial epiphyses were enlarged, but there was no effusion into the joints. All movements of knees and ankles caused some pain. Slight bowing of the femora and tibiae resulted in one inch of genu varum deformity. The secondary sex characteristics were well developed.

The following investigations were made during his first admission to hospital in 1933 :

URINE : Pale ; specific gravity 1001 to 1006. Trace of albumin (less than 0·01 gm. per 100 c.c. by Aufrecht's method). No red blood cells or casts.

WASSERMANN AND SIGMA REACTIONS : negative.

BLOOD : Urea 80 mgm. per 100 c.c. ; serum calcium 8·8 mgm. per 100 c.c. ; plasma phosphorus 6·75 mgm. per 100 c.c. ; phosphatase 0·97 units. (Kay's method.)

A calcium balance which was carried out at this time gave an unsatisfactory result owing to severe constipation. An intravenous pyelogram showed such poor excretion of the dye that it was impossible to draw any conclusions regarding the condition of the renal pelves or ureters. An x-ray examination of the bones showed evidence of active disease and the changes observed are described in detail below.

In September, 1933, he was re-admitted on account of occasional headaches and vomiting. The general condition was little changed, except for an increase of 13 lb. in weight and some dryness of the tongue. On admission his appetite was good and he did not feel ill, but two weeks later began to suffer from anorexia, nausea and attacks of vomiting. The blood urea, in spite of a diet containing only 30 gm. of protein, had increased to 224 mgm. per 100 c.c. He gradually became worse, with increasing drowsiness and vomiting, until, three weeks after admission, the blood urea was 400 mgm. per 100 c.c. and the clinical

picture, with its deep abdominal breathing, was typical of uraemia and acidaemia. At this stage of the illness a large dose of alkali was given by mouth, 1·3 gm. (20 grains) each of magnesium oxide and sodium bicarbonate three

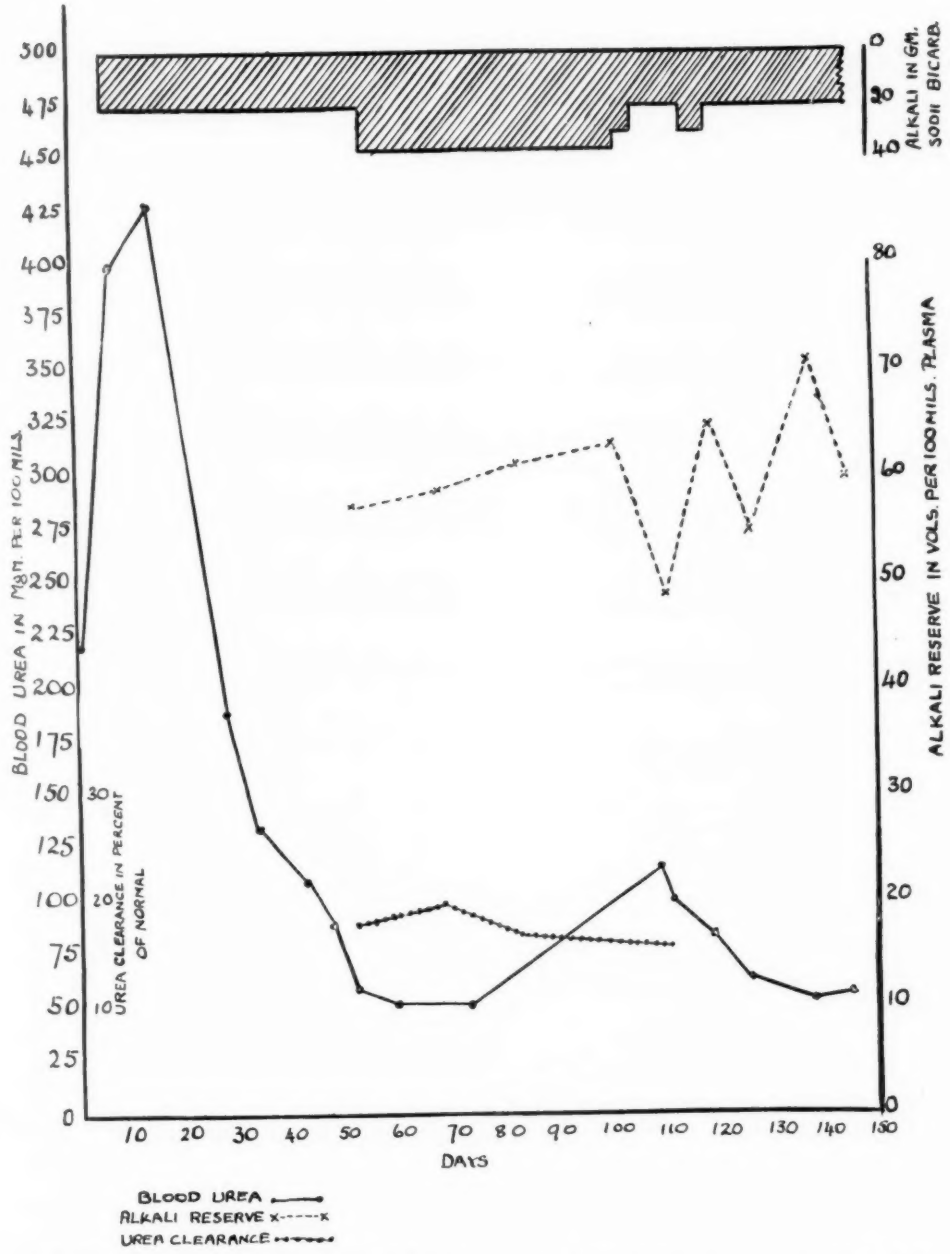
ALKALI IN GM. SODII BICARB.
BLOOD UREA IN MGM. PER 100 MILS.
UREA CLEARANCE IN PERCENT OF NORMAL
ALKALI RESERVE IN VOLS. PER 100 MILS. PLASMA
DAYS
BLOOD UREA
ALKALI RESERVE
UREA CLEARANCE

FIG. 1 shows the changes in the blood urea •——• alkali reserve ×———× van Slyke's urea clearance •–•–•–•–•–•–• and the dose of alkali ////// in case 1.

times a day, or the equivalent of 20 gm. of sodium bicarbonate. The blood urea increased slowly for a further six days and reached the maximum figure of 430 mgm., but during the subsequent two weeks it fell to 190 mgm. and

by the end of a further four weeks of alkaline treatment had decreased to 60 mgm. per 100 c.c. The daily output of urine rose from 950 c.c. to over 2,000 c.c. during the first ten days, after the administration of alkalis. The general condition of the patient improved rapidly during this time, although he had lost 13 lb. in weight and his haemoglobin had fallen from 95 to 58 per cent. in the two months.

In view of this remarkable improvement in the function of the kidneys with the alkaline treatment, an attempt was made to determine the reaction at which maximum renal efficiency was obtained. Parallel estimations of blood urea, alkali reserve, and van Slyke's urea clearance test were made while the dosage of alkali was increased or decreased. The lowest blood urea figures were obtained when the alkali reserve was between 59 and 61 vol. CO_2 per 100 c.c. ; when the alkali reserve fell to 49 vol. CO_2 per 100 c.c. the blood urea rose to 102 mgm. per 100 c.c. The amount of alkali needed to keep the alkali reserve about the optimum level was equivalent to approximately 20 gm. of sodium bicarbonate, and was given in the form of 1·3 gm. (20 grain) each of sodium bicarbonate and magnesium oxide three times a day. Simultaneously with the attempt to determine the optimum dose of alkali a specific treatment for the rickets was started. A large dose of vitamin D, 3,000 units, together with 15,000 units of vitamin A and 3 gm. of calcium lactate, was given by mouth, and this dosage was maintained for the next sixteen months. During this period the patient grew 6 inches and striking changes occurred in the bones (see later).

Although the amount of calcium deposited in the bones had increased by May, 1935, it did not seem adequate, especially as the patient was growing so rapidly. The dose of vitamin D was therefore increased to 6,000 units and that of vitamin A to 30,000 units, the dose of calcium lactate being kept constant. During the next nine months the patient grew a further $1\frac{1}{4}$ inches. From March, 1934, to September, 1936, treatment was carried out as an out-patient except for one admission in 1935 for the purpose of repeating the chemical and radiological investigations. The blood urea was estimated at intervals and was usually between 70 and 96 mgm. It was once as low as 58 mgm. and once as high as 132 mgm. per 100 c.c. The van Slyke urea clearance test was estimated several times and varied between C.M. 13 per cent. and C.M. 19·9 per cent., and was no worse after three years. The alkali reserve varied between 56 per cent. and 67 per cent., but there was no direct relation between the height of the blood urea and the alkali reserve. The haemoglobin was 95 per cent. before he developed uraemia, and it decreased to 58 per cent. following this illness. He was given large doses of iron at intervals, and the haemoglobin increased to 74 per cent., with a colour index of 1·0. A year later it was 61 per cent.

In September, 1936, he was re-admitted to hospital with the following history. Six days before admission he had felt unwell and had lost his appetite. Three days before admission puffiness of the eyelids was noticed, together with general oedema. Shortness of breath and cough started about this time. Both the oedema and the dyspnoea increased considerably. On admission he was pale and presented the picture of severe nephrosis with general oedema, ascites and rales at the bases of the lungs.

URINE : Specific gravity, 1005 ; fair amount of albumin (considerably more than on previous admissions) ; no red blood cells or casts.

BLOOD : Urea 210 mgm. per 100 c.c. ; alkali reserve 43 vol. (the usual amount of alkali had been taken) ; haemoglobin 32 per cent. ; plasma proteins 5·5 gm. per 100 c.c.

Atropine sulphate 1/100 grain was given subcutaneously on account of the oedema of the lungs and 300 c.c. of 6 per cent. sodium bicarbonate solution

was injected intravenously, thus raising the alkali reserve to 57·4 vol. per 100 c.c. Later in the day an intravenous injection of 50 c.c. of 25 per cent. glucose saline solution was given in order to increase the urinary output. The usual dose of alkali was given by mouth. Next day, in view of the severe degree of anaemia, the patient was given 600 c.c. of his father's blood without any unfavourable reaction, and the haemoglobin rose from 32 to 41 per cent. A short period of general improvement followed the transfusion, the oedema decreased and the blood urea fell to 128 mgm., but at the end of ten days he was not so well ; the blood urea had risen to 170 mgm. the alkali reserve being 69·1 vol. The alkali by mouth was therefore reduced by 1 gm. and the alkali reserve fell to 54·5 vol. and the blood urea to 132 mgm. On the twentieth day after admission the haemoglobin was 35 per cent. and a transfusion of 700 c.c. of group IV blood was given, the patient belonging to group II. Direct grouping showed no agglutination and nearly an hour was taken over the transfusion. Immediately after this he complained of shortness of breath and became restless. Many moist rales were heard all over the lungs. Atropine 1/100 grain, was injected, but he became rapidly worse with increasing dyspnoea and much frothy sputum. Oxygen, a further injection of atropine 1/50 grain and a venesection of 600 c.c. of blood produced a temporary improvement, but in less than two hours the patient died of acute pulmonary oedema.

Pathological examination.—A necropsy was performed sixteen hours after death by Dr. H. A. Magnus. The body was well nourished and measured four feet nine inches in length. Rigor-mortis and hypostasis were present. There was no lumbar cushion and no oedema of the legs.

Skeleton : There was no bossing of the skull, which was of normal thickness and density, and the vertebral column showed no deformity. There was some thickening of the costo-chondral junctions, but the ribs broke with the greatest difficulty. The ends of the long bones were thickened in the regions of the epiphyses and the femora and humeri were bowed. The epiphyseal lines were irregular but the bone was hard.

Cardio-Vascular System : The pericardium was natural. The heart weighed 328 gm. The auricles and ventricles were not dilated and there was no hypertrophy of the left ventricle. The valves and coronary arteries were normal and no atheroma or calcification was present in the aorta or smaller arteries.

Respiratory System : The pharnyx was normal and the tonsils were small and contained no pus. Small serous effusions were present in both pleural cavities and there were numerous sub-pleural petechial haemorrhages. The larynx, trachea and bronchi contained a large amount of frothy fluid and the lungs were filled with oedema fluid which poured out on section.

Peritoneum and Alimentary Tract : The peritoneal cavity contained one and a half pints of serous fluid. There was no evidence of peritonitis. The whole of the alimentary tract was normal and there was no evidence of uraemic colitis.

Liver, Spleen, Pancreas, Gall-bladder and Ducts : The liver weighed 1,805 gm. It was firm in consistency and normal in appearance. The spleen weighed 155 gm. and showed no naked-eye abnormality. Neither the spleen nor the liver contained any free iron. The pancreas and gall-bladder and ducts were normal.

Ductless Glands : The pituitary, thyroid, suprarenals and testes were normal. Four parathyroid glands of normal size were found.

Brain and Spinal Cord were normal.

Urinary System : The bladder was dilated and hypertrophied, and showed well-marked trabeculation. No stricture was present in the urethra and a sound was passed down the urethra into the bladder with ease, but unfortunately it

was not passed from the bladder to the penis. A careful dissection by Mr. W. E. Underwood subsequently showed that the prostatic urethra was dilated and that a small valve of mucous membrane was present distal to the verumontanum. The prostate gland was normal. Both ureters were dilated and their walls thickened, but the ureteric orifices were normal.

The kidneys were extremely small ; the left weighed 35 gm. and the right 30 gm. The capsules stripped easily leaving coarsely granular surfaces. It was difficult to define any cortex at all on the cut surface of the kidney, but in a few places it could be made out blending with the underlying medulla without any clear line of demarcation. The blood vessels were not unduly prominent and there was no increase in the amount of intrapelvic fat. Both pelves were dilated but there was no suggestion of pyelitis.

Histological examination.—Microscopic examination of all the organs, apart from the kidneys, showed no abnormality.

KIDNEYS : The appearances were those of a chronic focal glomerulonephritis in which there was extensive destruction of glomeruli and an equally extensive hypertrophy of the surviving glomeruli and their tubules. Associated with this there was a moderate degree of subacute intra-capillary glomerulitis, suggesting that, in addition to the chronic process, there had been a subacute exacerbation. Glomeruli could be seen in every stage of destruction up to complete fibrosis, but the capillaries of the surviving glomeruli were considerably obstructed by collagenous thickening of the sub-endothelial connective tissue. There was a well-marked diffuse interstitial fibrosis in which large numbers of completely atrophied tubules could be seen. A moderate amount of neutral fat was present, mainly in the glomeruli, but lipoid was absent, and no collections of cystine crystals were seen. There was no change in the medial coat of the arterial walls such as accompanies hypertension, but many arteries especially those of the calibre of the inter-lobular arteries, showed well-marked endarteritis obliterans of the type found associated with any chronic inflammatory process.

X-ray appearances.—The radiological appearances in renal rickets were divided by Parsons (1927) into three main types : atrophic, florid and woolly, stippled or honeycomb. Teal (1928), who had worked with Parsons, came to the conclusion that he could not make any real distinction between atrophic and florid types. Brailsford (1935), has confirmed this view and suggested that the types should be called A and B. In type A, which includes the atrophic and florid types, the calcification of the bone itself is comparatively normal, while in type B, which includes the stippled or honeycomb type, the calcification is deficient. This classification will be used throughout.

On admission in April, 1933, the following x-ray appearances were present :

SKULL showed absence of trabeculation of the cancellous bone of the vault but normal sutures. The cranial sinuses were not pneumatized and the longitudinal diameter of the pituitary fossa was small for the age of the patient : longitudinal, 10 mm. ; vertical, 9 mm. ; interclinoid, 6 mm.

The dentition was fair and up to the age of the patient except for the fact that the root canals were patent in the molar region.

VERTEBRAE were as for a child of eight years.

The most typical changes were found in the wrists and knees. The WRISTS (fig. 4*a*) showed changes of the A type of renal rickets. The cortex of the radius and ulna and the outlines of the epiphyses, even on the metaphyseal side, were comparatively good, but the metaphyses of both bones showed the concave cupping and splaying as well as the irregularity which is characteristic of the disease. The calcium content of the trabeculae appeared to be fairly normal, and there was a moderately good distinction between the cortex and the cancellous bone.

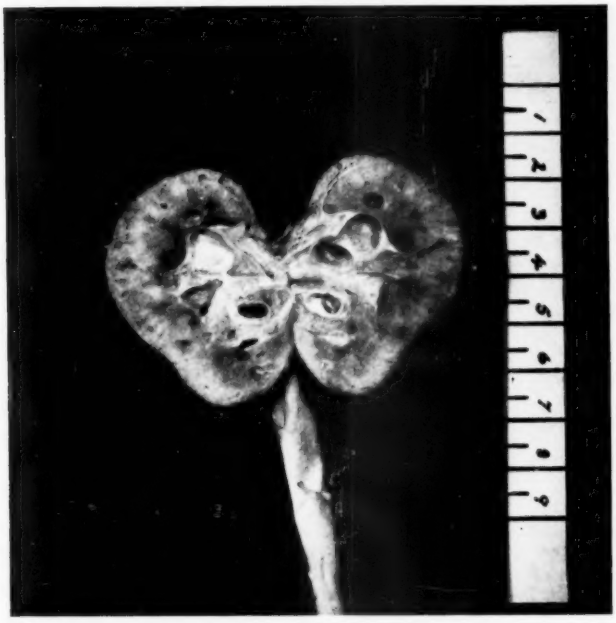

FIG. 2.—Photograph of the kidney split.

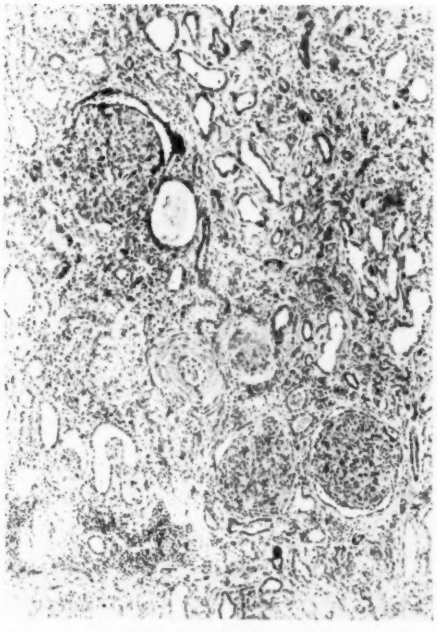

FIG. 3.—Microphotograph of the kidney.

FIG. 4*a*.—X-ray of wrist in April, 1933.

FIG. 4*b*.—X-ray of wrist in October, 1934.

FIG. 4*c*.—X-ray of wrist in June, 1935.

FIG. 5b.—X-ray of knee in October, 1934.

FIG. 5a.—X-ray of knee in April, 1933.

FIG. 5*c*.—X-ray of knee in June, 1935.

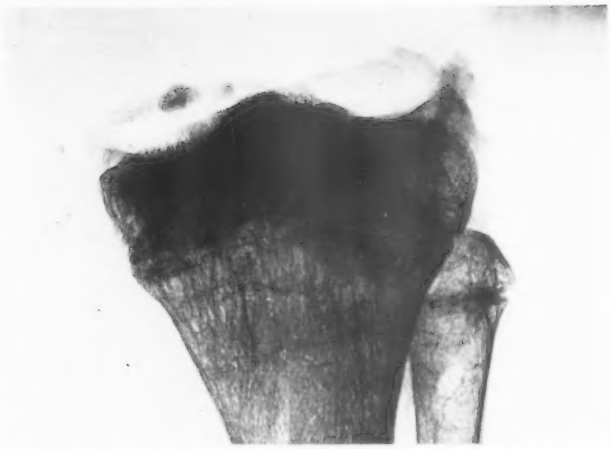

FIG. 5*d*.—Tibia after death in October, 1936.

FIG. 6.—X-ray of humerus in April, 1933.

KNEES (fig. 5*a*) : The changes in the knees, especially in the upper end of the tibiae, were also of the A type, but the calcification was more marked and there was some loss of distinction between the cortex and cancellous bone. Other interesting radiological appearances included a marked coxa vara deformity due to bending of the neck of the femur on both sides and incomplete fusion of ischium and pubis such as is seen in the normal child of eight. There was a varus deformity at the proximal end of the humerus (fig. 6) which also showed gross rickety deformity. In October, 1934, after eleven months' treatment, both wrists (fig. 4*b*) and knees (fig. 5*b*) showed an increase in the depth of the sub-metaphyseal irregular area, the degree of calcification remaining about the same. In June, 1935, there was narrowing of the epiphyseal line of the tibiae (fig. 5*c*) and a pseudocystic area due to trabecular absorption in the proximal end of the fibula. The calcium content of the bone had improved. The wrists (fig. 4*c*) showed similar changes.

At this time a small cystic area was noted in the distal end of the diaphysis of the fourth right metacarpal bone. In November, 1935, the wrists and knees showed no appreciable radiological change. In October, 1936, an x-ray of the tibia (fig. 5*d*) taken after death showed further narrowing of the epiphyseal line with commencing union. Trabeculation in the sub-metaphyseal region was nearly normal, the cortex was wider and the degree of calcification much greater than in the previous skiagrams.

FEMUR (decalcified) : A section through the lower end of a femur did not show any evidence of active rickets. The epiphyseal line was somewhat irregular but ossification was taking place normally.

Calcium and Phosphorus.—The results of individual estimations of serum calcium and plasma inorganic phosphorus of the two balance experiments are shown in table 1 and figs. 7–10. From these it will be seen that the calcium is low throughout, the lowest figure being 7·9 mgm. and the highest 9·3 mgm. ; the phosphorus was high before the treatment was started, the maximum being 6·75 mgm. and the lowest figure was 2·0 mgm. per 100 c.c.

TABLE 1

DATE	SERUM CALCIUM, MGM. PER CENT.	PLASMA INORGANIC PHOSPHORUS, MGM. PER CENT.
9/4/33	8·8	6·75
5/10/33	7·9	6·2
4/2/34	9·3	4·0
14/3/35	8·0	2·0
7/6/35	8·0	4·4

The calcium and phosphorus balance was estimated in May, 1934, before he had developed uraemia, but the figures are unreliable as the patient was constipated. The second calcium and phosphorus balance was carried out in March, 1934, about five months after the patient had recovered from uraemia. The blood urea was 55 mgm. per 100 c.c. blood ; the alkali reserve was 71 vol. of CO_2 per 100 c.c. blood ; the serum calcium was 9 mgm. and the plasma phosphorus 3·7 mgm. The calcium intake was 889 mgm. in the food (calculated) with an additional 376 mgm. in the form of calcium lactate = 1,265 mgm. The average output in the first four days was 1,230 mgm., giving a retention of 35 mgm. per day. In the second period of four days the amount excreted in the faeces was less and the average excretion was 1,046 mgm. and 119 mgm. of calcium was retained each day. The amount of calcium excreted in the urine was 10·5 per cent. and 8·5 per cent. of the total excretion in the two periods respectively.

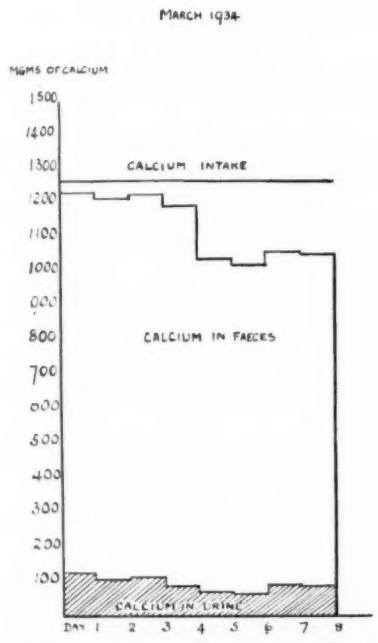

FIG. 7 shows the calcium balance in March, 1934.

Calcium in food	.. ..	889 mgm.
Calcium lactate	.. ..	376 mgm.
	Total	1,265 mgm.
Serum calcium	.. ..	9 mgm.
Plasma inorganic phosphorus		3·7 mgm.
Blood urea	.. ..	58 mgm.
Alkali reserve	.. ..	71 vol.

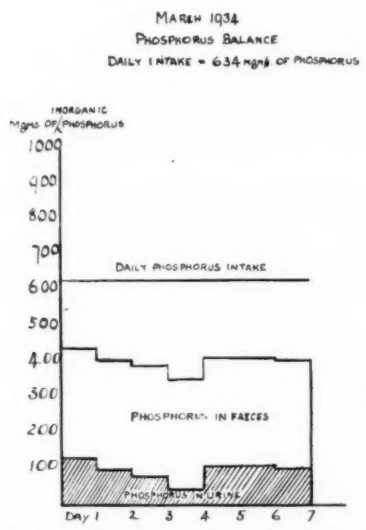

FIG. 8 shows the inorganic phosphorus balance in March, 1934.

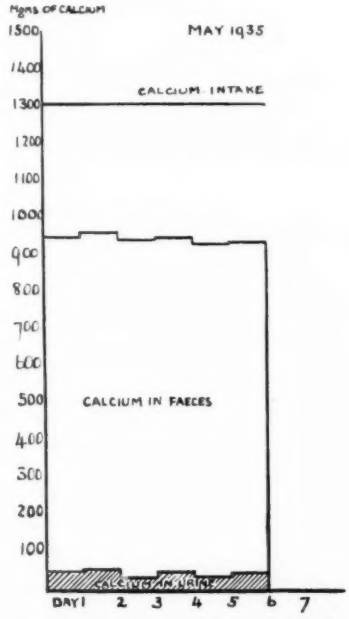

FIG. 9 shows the calcium balance in May, 1935.

Calcium in food	.. ..	931 mgm.
Calcium lactate	.. ..	376 mgm.
	Total	1,307 mgm.
Blood urea	.. ..	72 mgm.

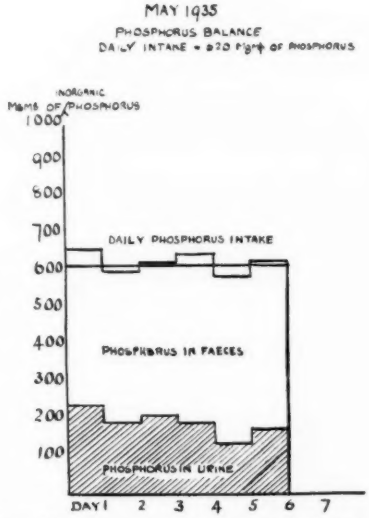

FIG. 10 shows the inorganic balance in May, 1935.

The inorganic phosphorus balance showed that the average amount of phosphorus excreted in the first three days was 418 mgm., giving a retention of 216 mgm. ; in the next four days the average excretion was 400 mgm. and 234 mgm. were retained. The percentage amount of phosphorus excreted in the urine was 25·6 per cent. and 24 per cent. respectively.

The third calcium balance was carried out fourteen months later. The blood urea was 72 mgm. per 100 c.c. blood. The calcium and phosphorus were unfortunately not estimated at the time the balance was carried out, but two months earlier the serum calcium was 8 mgm. and the plasma phosphorus 2 mgm., and one month later the calcium was 8 mgm. and the phosphorus 4·4 mgm. per cent. The calcium intake in the food had been increased to 931 mgm. (calculated) while the calcium lactate was still 376 mgm., total 1,307 mgm. The balance had altered considerably, as the small positive balance of 35–114 mgm. a day had been converted into a large positive balance of 407–419 mgm. The output of calcium in the urine had decreased by about 40 mgm., while the output in the faeces had decreased by over 265 mgm. and was responsible for the positive balance.

For the third phosphorus balance the intake was 620 mgm., which was slightly less than before. The average output for the three day periods was 640 and 626 mgm., so that a small negative balance was present instead of the positive balance of 234 mgm. fourteen months earlier. This change is partly due to the increase of the phosphorus excretion in the stools from 300 mgm. to 440 mgm. and partly to the increase in the average urine excretion from 100 mgm. to 191 mgm. The percentage amount of phosphorus excreted in the urine rose from 25·6 per cent. and 24 per cent. to 33 per cent. and 27 per cent. respectively. These figures are very low, as the percentage in the urine in health is usually over 50 per cent. Boyd Courtney and MacLachlan (1926) estimated the output in seven children with severe nephritis, and found that the percentage amount excreted in the urine was just over 50 per cent. in three cases, 43 to 40 per cent. in two cases, 28·6 per cent. in one case and 11·6 per cent. in one case. The amount of phosphorus in the diets was much larger than in the present case, as it varied from 1,250 to 2,200 mgm.

Case 2, A. B., aged seven years, was admitted to St. Bartholomew's Hospital in May, 1936. Born at term of healthy parents, he weighed $4\frac{3}{4}$ lb. at birth. was breast fed for nine months and was always small. He cut his first tooth at seven months, but did not sit up until eleven months. At eighteen months he crawled well, but his legs were beginning to bend, and he was not able to stand until he was three years old. At the age of five he was admitted to the Royal National Orthopaedic Hospital, and the following estimations were made.

URINE : Pale ; specific gravity was low.

BLOOD : Urea 160 mgm. per 100 c.c. ; calcium 7·1 mgm. per 100 c.c. ; phosphorus 6·9 mgm. per 100 c.c.

He was in hospital for two months and was discharged with splints for his legs. In the last two years he has walked about and been fairly active in spite of the bending of the legs. In May, 1936, he was admitted to St. Bartholomew's Hospital for treatment on the same lines as the first case.

CONDITION ON ADMISSION : He was a small boy, aged seven, weighing 22 lb., or 28 lb. under the average weight for a boy of his age. It was impossible to measure his height accurately on account of the bending of his legs. When these had been straightened by December, 1936, his height was $37\frac{1}{4}$ inches, or $8\frac{3}{4}$ inches under the average height. His head was well shaped and measured $18\frac{1}{2}$ inches. The milk teeth were intact, except for the lower incisors, but they were all loose and a moderate amount of pyorrhoea was present. The chest

was pigeon-shaped and the bending of the ribs was well marked. The arms were well proportioned, but the epiphyses of the wrists were large. The thighs were normal, but the tibiae were bent outward, and the internal malleoli were nine inches apart. The heart was not enlarged and the blood pressure was 110 mm. Hg systolic and 70 diastolic. His intelligence was poor, as he did not know his alphabet or numbers. He was observant and easily learnt to do things with his fingers, but he was either unable or would not concentrate on any lessons. His appetite was small and fanciful. The usual protein intake by choice was about 18 gm.

SPECIAL TESTS.

URINE : Pale, like water ; specific gravity, 1,005 ; trace of albumin ; no casts or cells seen.

The van Slyke urea clearance test was 10 per cent. of normal. Alkali reserve 45·8 vol. per 100 c.c. Serum calcium 5·8 mgm. per 100 c.c. Plasma inorganic phosphorus 3·4 mgm. per 100 c.c.

The general condition had changed very little in the last two years, except that the plasma phosphorus was now below normal limits instead of being raised. The bones showed well-marked changes of renal rickets. No investigations of the urinary tract were made, as it was thought that an intravenous pyelogram would be of no value as the urine was so dilute, and that a retrograde pyelogram with its attendant risks of sepsis was too dangerous a proceeding in a patient whose blood urea was over 100 mgm. per 100 c.c.

Treatment. This was carried out on similar lines to that of case I. A large dose of vitamin D, 6,000 units, together with 30,000 units of vitamin A was given. The alkali reserve was raised to normal with an alkaline powder containing calcium carbonate. Considerable difficulty was experienced in making him take these powders regularly, but after two months a mixture of bismuth carbonate, 0·33 gm. ; magnesium oxide, 0·33 gm. ; sodium bicarbonate, 0·66 gm. ; and sodium citrate, 0·66 gm. was given four times a day. The mixture was equivalent to 12·4 gm. of sodium bicarbonate. Through an oversight no additional calcium was given until March, 1937, when 3 gm. of calcium lactate was added.

The alkali reserve was easily raised above 60 vol. and has occasionally been as high as 70 vol. The blood urea fluctuated in a very extraordinary manner, and varied between 70 mgm. and 190 mgm. per 100 c.c. These changes were sometimes associated with obvious causes like dental extractions, but as a rule no other ailment was present. He had a considerable amount of pain and discomfort during the process of stretching of the external lateral ligaments of the knee-joints and bending the tibiae straight. He often appeared unwell with loss of appetite when the discomfort was great, and it is possible that this discomfort was responsible for the fluctuation of the blood urea.

The legs were placed in a rack splint, and the screws were turned every day. After three months the legs were sufficiently straight to enable a caliper splint to be used, the pressure being maintained with bandages. The straightening has been due both to the stretching of the lateral ligaments, which now allow a play of three inches, and also to the bending of the tibiae. This bending is partly permanent, as can be seen in the x-ray, and partly temporary, as it disappears when the splint is removed. He has been anaemic all the time, as the haemoglobin has never been higher than 58 per cent. in spite of large doses of iron, and in May it had decreased to 48 per cent. and was 47 per cent. in July.

Some three weeks after leaving hospital he joined a party of boys from his village and raided a plum orchard. Although his appetite while in hospital was always very capricious, he ate many unripe plums. On his return home he

complained of feeling unwell. One hour later he had a little diarrhoea and vomited. He was put to bed and two hours later a doctor was sent for as he seemed very ill. When Dr. Hay arrived an hour later the boy was dead, the whole illness having lasted four hours. At the post-mortem examination the stomach still contained many unripe plums. Portions of liver, spleen,

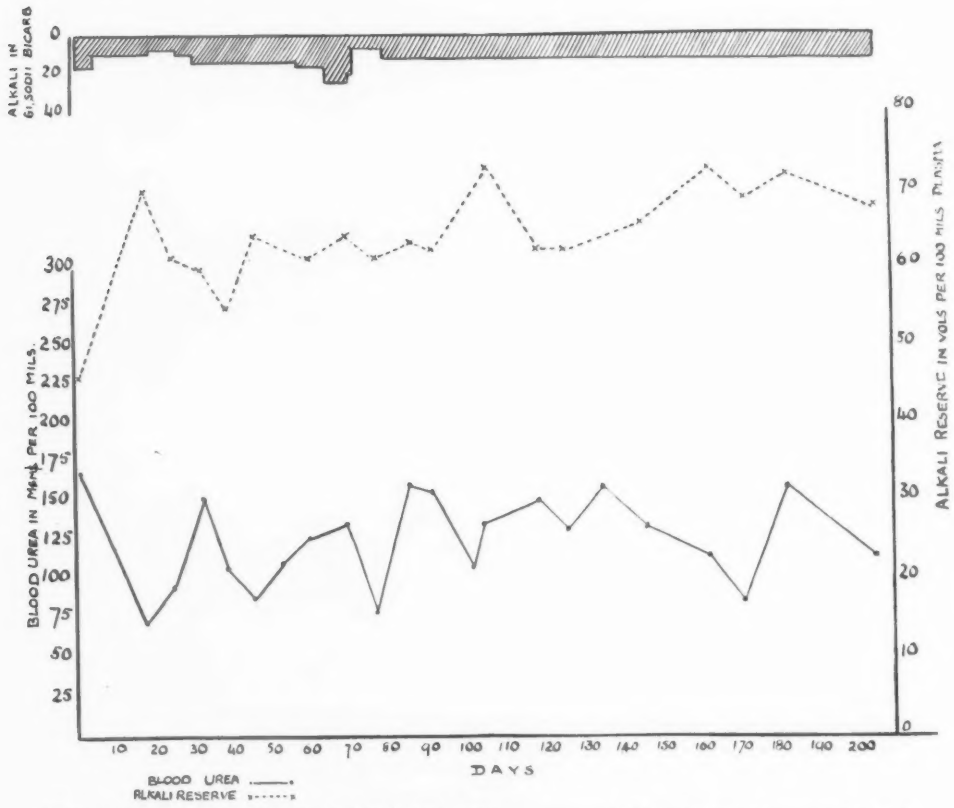

FIG. 11 shows the changes in the blood urea •———• alkali reserve × – – – × and dose of alkali ////////, in case 2.

pancreas, ulna bone and the urinary tract were sent to Dr. Magnus at St. Bartholomew's Hospital for histological examination.

Post-mortem examination.

The liver, spleen and pancreas showed no abnormality apart from fatty change in the liver and marked post-mortem change in all three organs.

The lower end of the ulna bone showed no macroscopic evidence of rickets and a longitudinal section through the epiphysis showed no evidence of active or healing rickets.

The kidneys, ureters and bladder had been removed in toto. The bladder was small but its wall was hypertrophied and trabeculated. Only one centimetre of the urethra was included in the specimen, but this showed no evidence of a stricture or of a urethro-vesical valve. The ureters were slightly dilated and their walls definitely hypertrophied. The kidneys presented a remarkable picture ; they were both very greatly reduced in size, the left weighing 12 gm.

FIG. 12*a*.—Knees not quite touching.

FIG. 12*b*.—Knees slightly overlapping.

Photographs taken in February, 1937, to show the amount of lateral movement permitted at the knee joints.

FIG. 12*c*.

FIG. 12*d*.

Photographs taken in July, 1937, to show the amount of lateral movement permitted at the knee joint.

FIG. 12*e*.—Photograph showing his appearance on discharge in July, 1937.

FIG. 13.

FIG. 14.

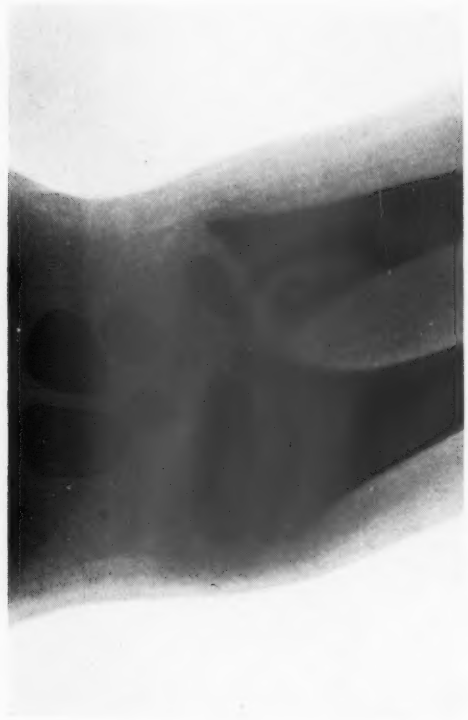

FIG. 15*b*.—X-ray of wrist in August, 1936.

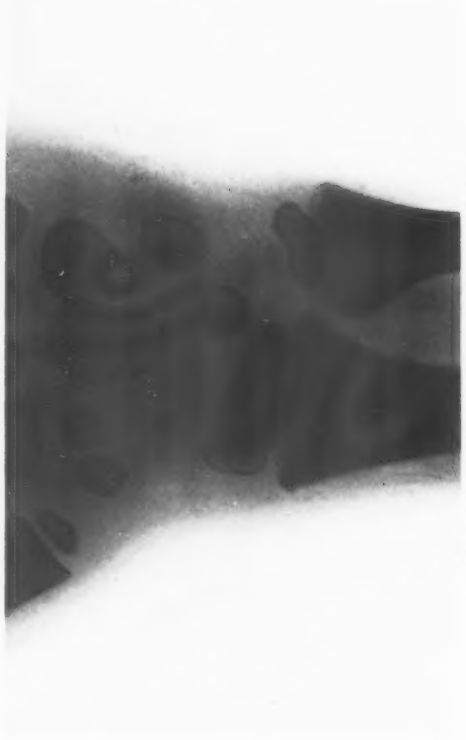

FIG. 15*d*.—X-ray of wrist in July, 1937.

FIG. 15*a*.—X-ray of wrist in May, 1936.

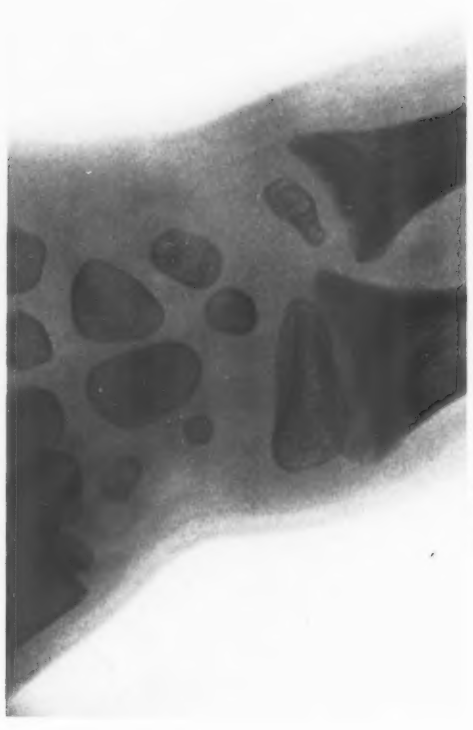

FIG. 15*c*.—X-ray of wrist in March, 1937.

FIG. 16*a*.—X-ray of both legs in May, 1936, showing bending of the knees.

FIG. 16*b*.—X-ray of both legs in March, 1937, showing the straightening of the legs.

FIG. 16*c* shows the state of the legs in July, 1937.

FIG. 17*b* shows the state of the knee-joint in July, 1937.

FIG. 17*a*.—X-ray of knee-joint in May, 1936.

and the right 15 gm. The capsules stripped easily, leaving smooth surfaces. The cut surfaces (fig. 13) showed slight dilatation of the pelves, which were surrounded by a very thin rind of kidney tissue in which no line of demarcation between cortex and medulla could be determined ; there were no retention cysts. The blood-vessels were not unduly prominent and there was no increase in the amount of intrapelvic fat.

Sections of the kidney (fig. 14) showed a different appearance from that observed in the previous case. There was a gross reduction in the amount of secretory tissue present in the cortex. The general picture was one of diffuse atrophy with no corresponding hypertrophy of surviving tissue. Although the few remaining glomeruli showed no striking alteration of structure, apart from patchy ischaemic obliteration, no scars of those that had disappeared could be identified. There was interstitial fibrosis, moderate in degree, in the cortex but becoming marked as the medullary portion was reached. In the patchy areas where glomeruli were few or absent there were focal accumulations of lymphocytes. There was no noteworthy change in the arteries beyond some increase in thickness of the internal elastic laminae.

The appearances in the kidney were not those of any type of Bright's disease, but were much more suggestive of the end result of a healed pyelonephritis of long standing.

The x-ray appearances in case 2 approximated more closely to the B type. The skull resembled that described under case 1 the pituitary fossa again being undersized : long diameter, 10 mm. ; vertical, 5 mm. ; and interclinoid, 6 mm.

The dentition, however, was backward, many milk teeth being present. The wrists (fig. 15*a*) showed the typical changes of cupping, splaying-out and irregularity of the metaphyses of the radius and ulna, but in addition there was marked decalcification of both bones and their epiphyses. The degree of epiphyseal development was that of a normal child of five. The long bones of both lower limbs (fig. 17*a*) also showed decalcification of the cortex and trabecular absorption, a severe degree of genu valgum being present owing to the bending of the tibiae and fibulae (fig. 16*a*) at the junction of the upper and middle thirds of both bones. Although the changes in renal rickets are usually more marked in the metaphyses than in the epiphyses, the proximal epiphysis of both humerus and femur in this case were more severely affected than the corresponding metaphysis. In August, 1936, after three months of treatment, the metaphyseal irregularity in the wrists (fig. 15*b*) and knees was greatly diminished and the cortex was well differentiated from the cancellous bone ; three new carpal bones had appeared and the calcium content of the bones as a whole was considerably improved. In January, 1937, the calcification had further increased, and the tibial epiphyses were better defined. In March, 1937, the bowing of the legs (fig. 16*b*) had decreased as a result of splinting, and three additional carpal bones (fig. 15*c*) had increased in size and the metaphyses had improved. In July, 1937, the metaphysis of the radius (fig. 15*d*) was better defined, the carpal bones and epiphyses showed normal increase in size for the period under consideration and the calcification had slightly increased. The tibiae (fig. 16*c*) showed a well-marked growth line below the epiphysis, but the degree of bending and calcification remained unchanged. In the region of the knee joint (fig. 17*b*) the epiphyses and general bony definition had also improved.

The calcium and inorganic phosphorus. The serum calcium was 5·8 mgm. per cent. on admission, but had risen to 9·8 mgm. during the year (table 2). The plasma inorganic phosphorus was 3·4 mgm. and varied from 3·1 to 5·0 mgm. during the year (table 2). It was impossible to estimate the calcium and phosphorus balance when the boy was first admitted as he was sometimes incontinent of urine. The first calcium balance was carried out in March, 1937, and

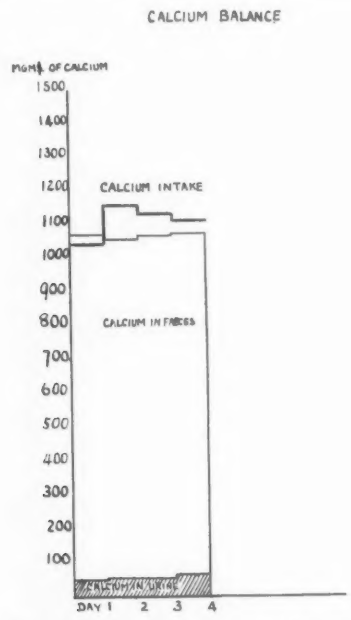

FIG. 18*a* shows the calcium balance in March, 1937 : calcium intake (average calculated), 1,110 mgm.

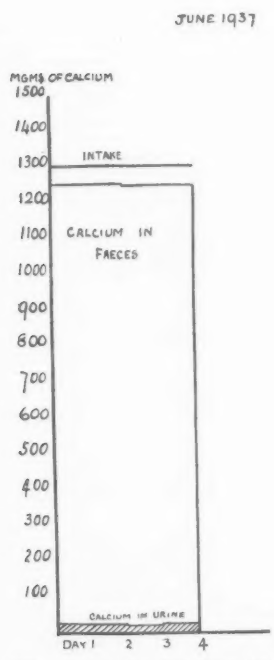

FIG. 18*b* shows the calcium balance in June, 1937.

Calcium in food	.. ..	924 mgm.
Calcium lactate	.. ..	376 mgm.
Total		1,300 mgm.

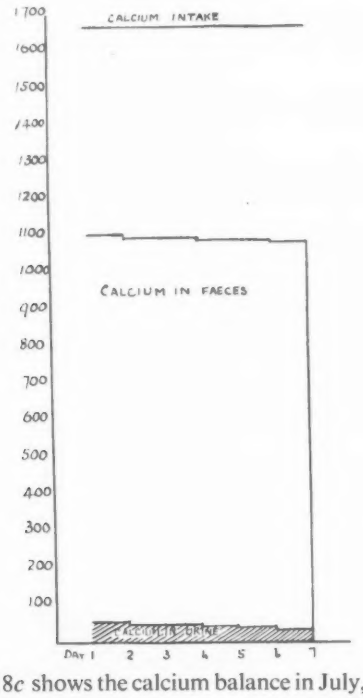

FIG. 18*c* shows the calcium balance in July, 1937.

Calcium in food	.. ..	1,288 mgm.
Calcium lactate	.. ..	376 mgm.
Total		1,644 mgm.
Serum calcium	.. .. ..	9·8 mgm.
Plasma inorganic phosphorus		3·4 mgm.
Blood urea	.. .. ..	124 mgm.
Alkali reserve	.. ..	64·3 vol.

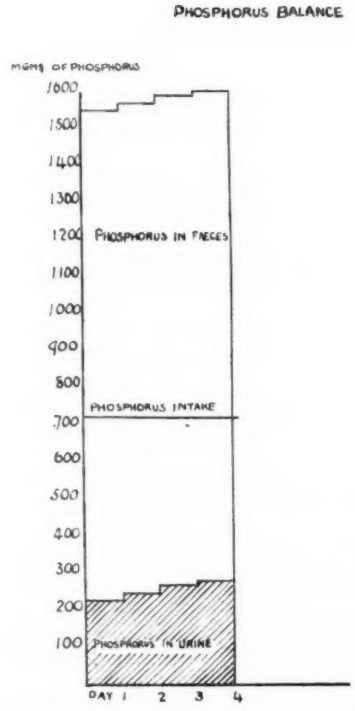

FIG. 19*a* shows the inorganic phosphorus balance in June, 1937 ; inorganic phosphorus (average intake), 723 mgm.

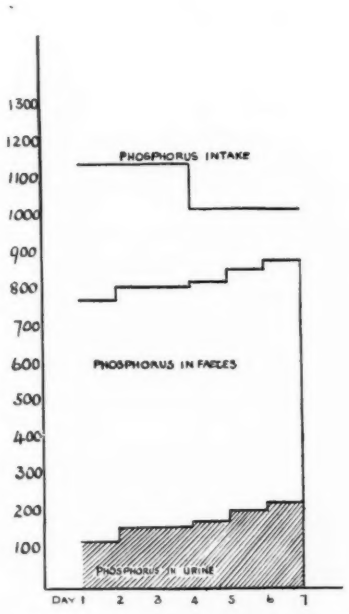

FIG. 19*b* shows the inorganic phosphorus balance in July, 1937 ; inorganic phosphorus (average of two periods), 1,090 mgm

owing to an accident in the collection of the stools the estimation for the first few days was spoilt. The average intake of calcium in the food was 1,110 mgm. (calculated) and the average total output was 1,069 mgm., giving a small positive balance of 41 mgm. a day. The urinary calcium was 54·6 mgm. or 5 per cent. of the total excretion. The inorganic phosphorus was unfortunately not estimated at this time.

TABLE 2

DATE	SERUM CALCIUM, MGM. PER CENT.	PLASMA INORGANIC PHOSPHORUS MGM. PER CENT.
12/5/36	5·8	3·4
10/7/36	8·8	4·0
14/1/37	8·8	3·1
8/4/37	10·6	5·0
23/4/37	9·4	—
23/6/37	10·3	3·8
15/7/37	9·8	3·4

The second calcium balance was carried out in April, 1937, when 3 gm. of calcium lactate had been added to the diet for four weeks. The test was not satisfactory, as the amount of food which he ate each day was variable, and the intake of calcium varied in consequence from 550 mgm. to 1,245 mgm. (calculated). The average for the four days was 926 mgm., making 1,302 mgm. with the 376 mgm. from the calcium lactate. The average output for the four days was 1,247, giving a small positive balance of 55 mgm.

The intake of inorganic phosphorus was variable : in the four days before the estimation of the balance it was 888 mgm. (calculated) and in the actual four days of the experiment was 723 mgm. (calculated) and varied from 421 to 960 mgm. The inorganic phosphorus excreted in the urine averaged 256 mgm. and, in the faeces, 1,321 mgm., making a total of 1,577 mgm. This gives a negative balance of 832 mgm. It is unfortunate that the intake was small and varied so widely from day to day. But the total excretion of the phosphorus in the urine and faeces is very large and much greater than that found in case 1 when the intake was rather smaller.

A third balance experiment was carried out in July. The dose of vitamin D had been increased to 9,000 units and the vitamin A to 45,000 units to aid the recovery from an attack of acute tonsillitis and was maintained at this figure partly because the positive balance of calcium had been only 55 mgm. in the second balance and partly because he was growing fast. The blood urea was 124 mgm. ; the alkali reserve was 64·3 vol. ; the serum calcium was 9·8 mgm. ; and the plasma phosphorus was 3·4 mgm. The boy was much less capricious over his food and the daily intake of calcium and phosphorus was much greater and varied little from day to day. The collection of the stools into two three-day periods was not satisfactory, as some mixing had obviously taken place, and figures for the six-day period are used. The average intake of calcium in the food was 1,288 mgm. (calculated) and 376 mgm. as calcium lactate, making 1,664 mgm. in all, which is an increase of 362 mgm. over the second balance experiment. The average total output per day was 1,074 mgm., giving a large positive balance of 590 mgm. The average urinary calcium was 42 mgm. or 3·9 per cent. of the total output.

The daily intake of inorganic phosphorus was 1,100 mgm., which is an increase of 380 mgm. per day. The average total output was 653 mgm., giving a positive balance of 254 mgm. in contrast to the negative balance

of 832 mgm. in the second balance. This change is partly due to the decrease in the urinary inorganic phosphorus from 256 mgm. to 182 mgm., but mainly to the decrease in the faecal inorganic phosphorus from 1,321 to 653 mgm. The percentage amount of inorganic phosphorus excreted in the urine was 22 per cent.

The figures for the serum calcium and plasma inorganic phosphorus and those for the final balance experiment suggested that the development of the bone could proceed normally, provided that no substantial change took place in the state of the kidney.

Discussion

The change in the condition of these two patients during the period of their supervision is great, and it is important to consider whether it is due to the alkalis or to the vitamin D. All other workers with the exception of György (1928), Duken (1928), Schick (1929), Karelitz and Kolomoyzeff (1932) have said that neither vitamin D nor ultra-violet light is of any value. György treated a girl aged ten who had such severe pains in her legs that she had to stay in bed. She was given 4–6 mgm. of vigantol daily for seven months. Within three months she was able to walk about, but the rachitic lesion had not completely healed in seven months. Duken (1928) treated a boy aged six with vigantol, 4 pastilles a day for thirteen days only, and, judging from the x-ray photographs good healing of the bones took place in the next six weeks. Both these patients suffered from gross infection of the urinary tract and, although no mention is made of treatment, it is possible that the usual treatment with alkalis was given. Karelitz and Kolomoyzeff (1932) treated a child aged six with 0·3 c.c. of vigantol daily for six weeks, and in the next twelve weeks definite healing of the bones began. A further course of 0·25 c.c. of vigantol for six weeks was terminated by an attack of mumps, which made her very ill. The condition of the bones became much worse and she died shortly afterwards. Treatment with alkalis is described by Schoenthal and Burpee (1930), who concluded that ' replacement of depleted base calcium and phosphate is a logical method of treatment, but the effects are but temporary unless the treatment is continuous. This may be accomplished by the administration of an alkaline ash diet together with calcium acetate.' They did not give any vitamin D and did not report any improvement in the bones. Karelitz and Kolomoyzeff (1932) approve of this form of treatment, but think that ultra-violet light might also help. Salvesen (1934) noticed an improvement in his patient's capacity for walking when he gave ultra-violet light and at the same time raised the alkali reserve with calcium lactate. Ultra-violet light by itself made the patient's symptoms worse, while the calcium lactate by itself caused an improvement. Two months after the calcium lactate was given x-ray examination did not show any change in the bones, and the patient died of uraemia one month later.

The alkali reserve was not estimated in the early cases, but Green (1922) found that it was lowered and his findings have been confirmed by many other observers : Lathrop (1926), Hertz (1929), Mikulowski (1930), Faxen (1932), Meier (1934–5), Debré, Marie, Dayras and Bernard (1935), Elliott (1933), Bader (1934), Shelling and Remsen (1935), and Roberts (1936). The alkali reserve in these cases is usually below 55 vol. of carbon dioxide per 100 c.c. blood, and may be as low as 20 vol. in patients dying of uraemia. Patients with severe kidney damage may be considerably benefited when the alkali reserve is raised to within normal limits. The ability of the kidney to excrete urea will often improve considerably if any septic focus is present which can be removed. This is especially the case after operation on the urinary tract.

The lesion of the kidney in renal rickets is a peculiar one as it tends to progress very slowly, and in the second case here reported the blood urea at the age of six was exactly the same as at the age of four. This is perhaps explained by the condition of the kidney in case 1, for whereas a great many tubules and glomeruli were destroyed the remaining ones were hypertrophied and presumably healthy before the last attack of nephritis associated with oedema. If the hypertrophied glomeruli and tubules are healthy and no superadded infection is present the excretion of urea should remain unaltered, and would explain why in case 2 the blood urea remained unaffected for two years. Since the excretion of urea is aided when the alkali reserve is within normal limits it is possible that the excretion of other substances like phosphorus is also improved. In case 1 the positive phosphorus balance of 234 mgm. was replaced fourteen months later by a small negative balance of 20 mgm., and the change is partly due to the increase of 90 mgm. of phosphorus excreted in the urine and partly to the increase of 140 mgm. in that excreted in the faeces. The positive calcium balance in the same time was increased from 35 to 410 mgm. In case 2 a large negative phosphorus balance occurring at a time when the calcium balance was just positive and the rickets was healing was converted fifty weeks later into a positive phosphorus balance at the same time as the positive calcium balance increased considerably. The lower output of phosphorus into the gut, which was detected once in both cases, is difficult to reconcile with one of the hypotheses, for the altered amounts of calcium and phosphorus in the blood. Mitchell (1930) suggested that the relative failure of the kidney to excrete phosphorus in the urine caused an increase in the inorganic phosphorus in the blood and an increased secretion of phosphorus into the gut. He thought that this excess of phosphorus in the gut caused a precipitation of the calcium of the food as an insoluble phosphate which was absorbed with difficulty. It is possible that this factor is important when the disease is developing, and that the action of the high phosphorus excretion into the gut in the present cases was prevented by the large doses of vitamin D and the alkalis.

There is no evidence as to whether the alkali or the vitamin D is really responsible as they were given simultaneously. It is possible that alkalis alone might enable the amount of vitamin D in an ordinary diet to effect the absorption of sufficient calcium though the recovery of the bones would be slow. The problem was also complicated by the use of a trade preparation of vitamin D

which contained a large amount of vitamin A, as it was hoped to improve the general health of the patients, and this may have played some part in the improvement.

Summary

Two patients with renal rickets have been treated with sufficient alkali to restore the alkali reserve to within normal limits, and at the same time with large doses of vitamins D and A. The general condition improved ; they grew in height and gained weight ; the state of the kidney was slightly improved ; the anaemia was little altered, while the condition of the bones was greatly improved.

Thanks are due to Dr. H. A. Magnus for his description of the post-mortem findings ; to Mr. W. E. Underwood for his dissection of the urinary tract ; to Dr. G. Simon for his reports on the x-ray examination of the bones, and Mr. S. L. Higgs for superintending the splinting of the limbs in case 2 ; to Mr. H. E. Archer for the many chemical estimations, and Miss Cambell, the Sister of the Ward, for her skill and care of both these patients.

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A CASE OF PERIARTERITIS NODOSA WITH SUBCUTANEOUS LESIONS AND RECOVERY

BY

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Periarteritis nodosa is the name given to a disease with a high mortality affecting the arterial system, characterized by a widespread destructive nodular arteritis which produces, by interference with the blood supply from occlusion and thrombosis, a variable clinical picture according to the organs or parts of the body most especially involved. The disease appears to be comparatively rare during early life and in only a minority of the cases are there lesions of the superficial tissues of the body. When this happens diagnosis during life becomes possible. The case about to be reported had superficial lesions in the form of a nodular erythema and during the earlier stages of the prolonged illness the vascular occlusion was sufficient to produce several areas of localized gangrene.

Rothstein and Welt (1933) reviewed the cases in children which have been reported up to 1932. With two of their own cases these number twenty-three of a total of one hundred and ninety-five cases mentioned by them at all ages. The majority of the cases have been reported in the American and German literature. In this country Barnard and Burbury (1934) have reported the case of a child of eight years whose illness terminated fatally after a course of eight weeks and who showed extensive peripheral lesions of the nature of painful cyanosis of the extremities and gangrene. The present case is unusual in that recovery took place after a prolonged illness made up of a series of recrudescences separated by varying periods of comparative freedom from symptoms. The course of this patient's illness resembled that of the child described by Lindberg (1931). It is possible that this form of the disease, characterized by superficial erythematous nodules, has a more favourable prognosis.

Case report

Mary H., aged seven years, is the eldest of four children. The three other children and the parents are alive and well. The medical history of the family is uneventful. There is no history of rheumatic disease. The patient was quite well until July, 1935, when she developed headache and fever. She was seen

by Dr. Cooke of Hunslet, Leeds, who found active tonsillitis. Nine days later she complained of generalized pains and there was redness and swelling of the left wrist. She was then admitted to St. James' Hospital, Leeds, as a case of acute rheumatism.

The whole illness lasted twenty-two months and comprised five phases of active illness of approximately five months, eight months, five weeks, three weeks and five weeks. The long phase of eight months was divided into two approximately equal parts by a brief interlude of three weeks during which the characteristic symptoms subsided and the temperature became normal. The child, however, was still listless and ill. The five phases of illness were roughly separated by quiescent intervals of eight weeks, six months, three weeks, and three weeks during which time the child was well and able to enjoy life.

The initial phase lasted from July 26, 1935, to September 4, 1935. The onset as noted above had the clinical aspect of an acute rheumatism. On admission to St. James' Hospital the child was obviously ill. There was active tonsillitis with difficulty in opening the mouth suggesting peritonsillar abscess. There was also generalized pain, specially evident when an attempt was made to move the limbs passively. During the early days in hospital she developed colicky abdominal pain and there was tenderness and rigidity of the abdominal wall sufficiently pronounced to suggest the possibility of a septic peritonitis. The stool contained blood and mucus. The urine contained a trace of albumin. The temperature was 101°–102° F. and pulse 120–140. The heart was not enlarged though its rate was rapid, and there were no bruits or pericardial friction. Ten days after admission there was oedema of the face and eyelids. By this time the illness had the aspect of a septic condition and the oedema suggested sinus infection. A month after the onset improvement began to show itself. The temperature became normal on September 4, and the symptoms subsided and she remained comfortable and appeared to be convalescent until November 5, when the second phase began. A throat swab taken during the early days was negative for B. diptheriae.

The second phase lasted from November 5, 1935, to the middle of July 1936. This phase also began with headache and sore throat. A patch of membrane appeared on the left tonsil and the throat swab was reported as positive for B. diptheriae. The child was then sent to the Seacroft Fever Hospital. The diagnosis was confirmed and she was shown to be Schick negative. No serum was given. The organism was classified as belonging to the intermediate type.

Within a few days of admission to Seacroft Hospital small red papules or nodes, slightly indurated to palpation, developed over both cheeks, the right eyelid, about the elbows and over the extensor surface of her knees. During the following weeks there were fresh crops of nodules over different parts of the body, such as the sacral region, the hands and wrist, the feet, the shoulders, the right groin and buttocks, over the front of trunk, and the right thigh. On February 27 there was a final outbreak of nodules over the knees, feet, elbows and forearms. The cycle of events in the development and subsidence of these nodules was as follows : each node was slightly raised, tender and gave the feeling of induration involving the tissues deeper than the skin. Around the nodes there were areas of spreading erythema which coalesced as the nodes aged. There was also deepening of colour to purple, producing a cyanotic appearance of the area involved. Subsequently there remained a more or less pigmented appearance giving a ' café-au-lait ' effect which persisted for some

weeks. During the early stages of the development of the erythematous nodes the appearance produced was not unlike that of erythema nodosum, but this appearance was quickly lost. The individual node was not thought to be so tender as that of erythema nodosum, although the area involved was generally hyperaesthetic, and this indeed was at times most pronounced, and with the pain in the limbs, especially with any movement, caused the child great discomfort. Coincident with the involvement of the looser tissues of the face there was local oedema. It was during this phase of illness that several small areas became gangrenous. This development was quite clearly a more advanced stage of the subcutaneous inflammatory process which was producing the lesions just described and which, with the exceptions to be mentioned, finally resolved without leaving permanent visible injury to the skin and underlying structures.

FIG. 1.—The symmetrical scars resulting from the two areas of superficial gangrene.

The points of local gangrene were as follows : two symmetrical areas behind the shoulders (fig. 1), which became black and crusted and the superficial tissue was finally shed with the formation of irregular whitish scars measuring approximately one-and-a-half inches across. Following a painful cyanotic swelling of the left index finger, the terminal phalanx became black and dead and finally separated, leaving the finger shortened by three-quarters of an inch (fig. 2). The end of the nose became blue, superficial gangrene took place and a small white indented scar resulted (fig. 3). A perforation of the nasal septum was discovered following brisk epistaxis.

The constitutional disturbance during this long phase of illness was severe. Great difficulty was met with in feeding her, and her appearance towards the end of the eight months was that of extreme marasmus. Listlessness and irritability were persistent throughout. A distressing symptom was obvious

FIG. 2. The shortened index finger.

FIG. 3.—The depressed scar resulting from the superficial gangrene of tip of nose.

discomfort when handled and when moved. Continuous flexion of the arms and legs was an interesting feature. There was almost continuous pyrexia during the whole period except for two intervals of four weeks and ten days during which the temperature was normal. From time to time there was swelling about several joints, but this was judged to be the result of the nodal erythematous formation about the joint rather than due to synovitis. The pulse rate was much increased throughout, and even during sleep remained about 120. It was felt that the rate was not entirely explained by the rise in temperature. The heart sounds remained clear, and the rather loud short first sound suggested dilatation. At no time was there bruit or friction. The blood pressure was 80 mm. Hg. systolic and 40 mm. diastolic. Towards the end of the phase the child had a mild stomatitis which was troublesome for two or three weeks.

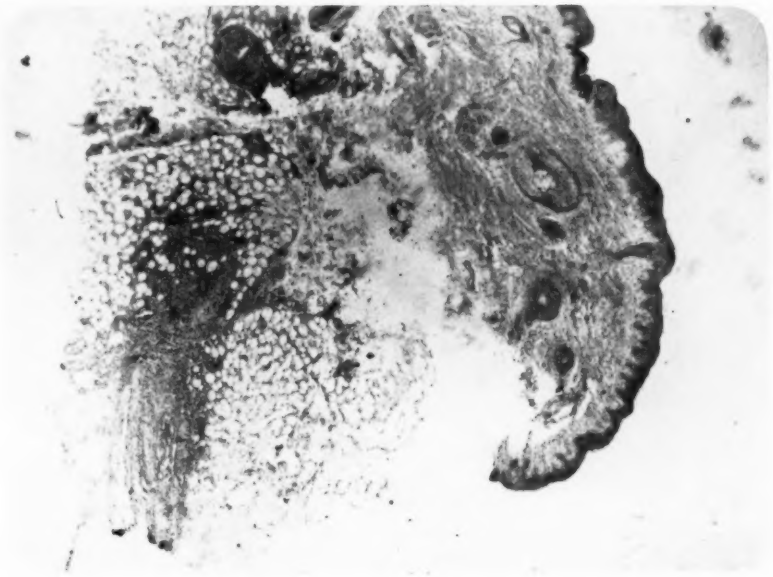

FIG. 4.

The child was considered convalescent towards the end of July and was then able to get up. Weight increased steadily. She was discharged from hospital at the end of September, her weight then being 50 lb. The first four months of the long phase of illness took place at Seacroft Hospital, the child being returned to St. James' Hospital on March 3 at the time when her active symptoms had subsided. While at Seacroft she was seen by Dr. John Ingram, Dermatologist at the Leeds General Infirmary, and he was the first to express the opinion that the child might be suffering from periarteritis nodosa.

The following are the chief examinations carried out during this period :

March 26 : White cells 8,400 per c.mm., neutrophil polymorphs 85 per cent., eosinophils 0·3 per cent., mast cells 0·3 per cent., lymphocytes 10 per cent., large hyalines 2·4 per cent. Wassermann test : negative.

April 23 : White cells 6,500 per c.mm., sedimentation rate : 1st hour, 140 mm. ; 2nd hour, 147 mm. ; 4th hour, 150 mm.

FIG. 5.

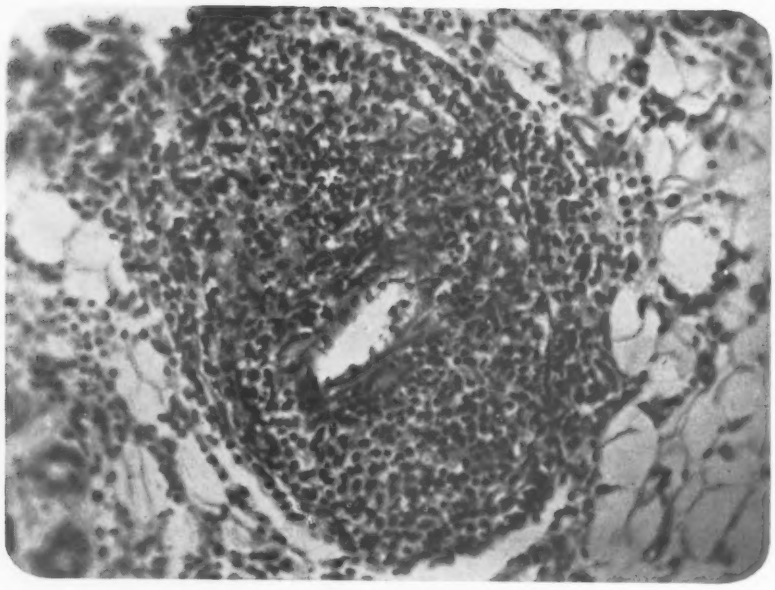

FIG. 6.

July 29 : White cells 14,500 per c.mm., neutrophil polymorphs 51·5 per cent., eosinophils 6 per cent., mast cells 1 per cent., lymphocytes 34 per cent. large hyalines 7·5 per cent.

On April 2 a nodule from the arm was removed and the following is the report : One of the subcutaneous nodules was excised for biopsy. It measured 5 cm. by 3 cm. (fig. 4). Swelling was due to localized inflammation related to two small arteries in the subcutaneous tissue (fig. 5) and also involving the intervening fatty tissue. The appearances of both these arteries were similar. One vessel, 3 mm. in diameter, was grossly destroyed by inflammation, so that only the single layer of endothelium forming the intima was recognizable (fig. 6). The internal elastic lamina was also intact. The wall of the vessel was widely infiltrated by cells of inflammatory type, the majority being polymorphonuclear leucocytes ; a proportion of these were eosinophilic. Fibrinoid degeneration was also apparent in the media.

The other vessel involved was approximately 7 mm. by 3 mm. and presented

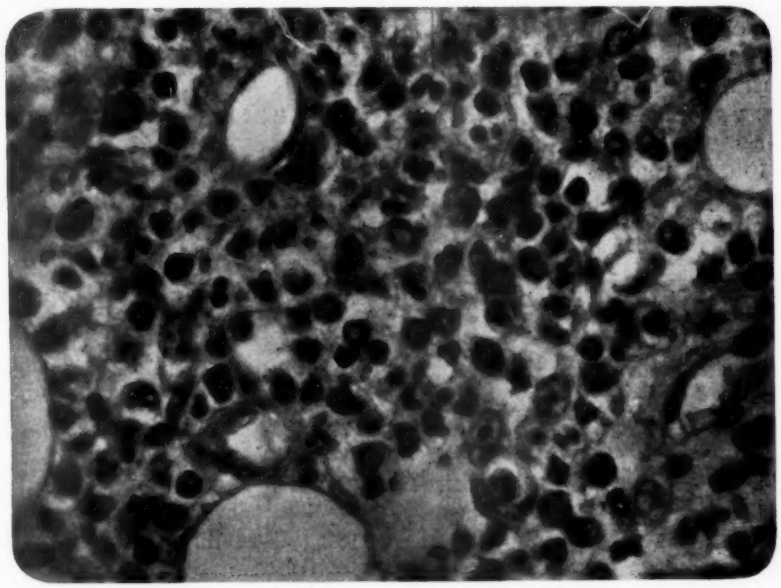

FIG. 7.

similar appearances, with the addition of thrombosis ; canalization of the clot had occurred. Eosinophilic infiltration in the neighbourhood of this vessel was particularly pronounced, accounting for approximately a third of the cells. There were a few plasma cells, and there was evidence of fibroblastic proliferation (fig. 7). These appearances were thought characteristic of periarteritis nodosa.

In the third phase the child remained perfectly well until December 16, 1936. Her feet then became swollen and painful and there was pain with movement of the hands. She was re-admitted to St. James' Hospital.

Her condition on admission was : temperature 101° F., pulse 128 and respiration 26. The tonsils were injected and swollen. There was tenderness over legs, specially about the feet and ankles, which were slightly swollen. The arms were flexed and the right shoulder was fixed and painful. There was patchy erythema over face, cheeks and neck with nodules scattered unevenly over this

area and over the arms, dorsum of hands and to a less extent over the trunk and legs. The degree of illness and prostration was not severe.

The nodules with their spreading erythema passed through the same stages of coalescing and tendency to deepen in colour as they aged. The pulse rate was again increased and ranged between 120 and 150. Even during sleep the pulse kept at 120. The general hyperaesthesia and pain in the limbs were again evident and the flexion at the proximal joints was repeated. A painful stomatitis was again troublesome, and on this occasion was much more severe and prolonged. There was no formation of membrane or obvious ulceration. Rather was the appearance one of acute swelling and congestion of the whole area of the mouth, accompanied by pronounced gingivitis of a painful character.

This phase lasted approximately five weeks. The temperature became normal by January 6 and the active and painful symptoms had disappeared by January 20.

The pathological investigations during this phase included : Blood examination : whites 22,900, per c.mm., polymorphs 85 per cent., lymphocytes 11 per cent., eosinophils 1 per cent., myelocytes 2 per cent. Sedimentation rate : 1st hour, 32 mm. ; 2nd hour, 47 mm. Blood culture negative. Throat swab : Staphylococci obtained on culture. Mouth swab : No spirochaete or fusiform bacilli seen.

There was an interval of three weeks during which the child remained comfortable and was able to sit up and take her food normally.

The fourth phase of illness began with repetition of the pyrexia and the development of nodal erythema over the arms and dorsum of the feet. On this occasion there was no general spread, nor was there tonsillar inflammation or stomatitis. There was, however, a recurrence of the pain in the limbs and flexion of the large joints. Within three weeks the child became free from active symptoms and remained well for three weeks.

The fifth and last phase was similar in its symptomatic presentation to the preceding one. It lasted, however, for five weeks and the nodal erythema was more widespread and the constitutional disturbance, while rather more severe, was not so intense as that experienced during the earlier phases.

Blood examination : reds 3,270,000 per c.mm., C.I. 0·9, Hb 60 per cent., whites 24,000 per c.mm., polymorphs 85 per cent., lymphocytes 14 per cent., eosinophils nil.

Sedimentation rate : 1st hour, 130 mm. ; 2nd hour, 141 mm. During the convalescent period a further test was as follows : 1st hour, 13 mm., 2nd hour, 37 mm.

The child was discharged from hospital during the third week in July and has remained well since (September, 1937).

Discussion

Only a small minority of the cases of periarteritis nodosa so far reported resemble this case. A diagnosis is rarely possible during life because so few patients have superficial lesions. In the majority the clinical picture is bizarre and most variable, and depends upon the disturbance in function of the organs involved. This is due, in the main, to the interference with the blood supply brought about by the arterial occlusion from intimal thickening and thrombosis, and in some cases by the resultant gangrene. The clinical picture may simulate closely nephritis (haematuria, albuminuria, increased blood pressure), acute abdominal disease (cramp, vomiting, diarrhoea, melaena), myositis (muscular

pains and tenderness), cerebral disease (hemiplegia from rupture of aneurysm), cardiac disease (quickened pulse, coronary occlusion), acute rheumatism (pain, tenderness, pyrexia), purpura haemorrhagica (subcutaneous haemorrhage, melaena), arterio-sclerosis (widespread vascular scarring and occlusion), or may take the form of this case.

The onset of the patient's illness suggested a rheumatic infection, although the acute abdominal symptoms and the blood in the stools during the early days and the oedema of the face and eyelids at the end of the first fortnight seemed to discount this provisional diagnosis. It was then thought that she was suffering from some septic infection and the facial oedema suggested sinus trouble. In the light, however, of the symptoms reported by other observers it is possible that the initial facial oedema was the result of the periarteritis nodosa of the subcutaneous vessels, and that the abdominal symptoms indicated like involvement of branches of the mesentèric vessels.

The diagnosis in the majority of reported cases has rested on the autopsy findings. The feature common to all these cases was widespread destructive arteritis of a patchy rather than diffuse type of sufficient severity to cause patchy necrosis of the vessel wall, occlusion and thrombosis. The nodular formation has been due to the massive local cellular infiltration of the adventitia or in some cases to the formation of multiple small aneurysms. These striking pathological features have lead to the belief that periarteritis nodosa is a disease caused by a specific etiological agent. The question, however, has been frequently raised if it is not possible that some of the reported cases are examples of arterial damage produced by different agents, and not necessarily by the specific agent, which, in the case of periarteritis nodosa is claimed to be a filtrable virus.

The Wassermann reaction is rarely positive. A positive reaction was observed by Bernstein (1935), in whose patient periarteritis nodosa was proved by biopsy of muscle tissue. Ophüls (1923), who discussed this fully, points out how closely some of the arterial lesions copy those of syphilis. The treponema pallidum has been looked for in the acute severe lesions of the disease and they have never been found. The pronounced polymorphonuclear infiltration in periarteritis nodosa, a striking feature, seems also to discount a syphilitic infection.

The interesting and not infrequent association of periarteritis nodosa with acute rheumatic fever has been noted on several occasions. Ophüls (1923) refers to this, but expresses the opinion that the two processes are different clinically and pathologically and are to be easily differentiated. Rothstein and Welt (1933) described a boy of seven years who at post-mortem had a subacute verrucous rheumatic endocarditis with typical Aschoff nodes in the heart muscle. Widespread lesions of periarteritis nodosa were also present. Friedberg and Gross (1934), in reviewing eight cases of the disease, found Aschoff nodes in the myocardium of four of the cases. One of the cases had suffered from acute chorea and at post-mortem there were found acute myocardial and endocardial rheumatic lesions associated with widespread lesions of periarteritis nodosa. These lesions involved the arteries of the lungs and

kidneys and the external iliac and the coronary arteries. During life the clinical picture had been that of an acute rheumatic affection. They also refer to several other cases in which the association was revealed at post-mortem. In submitting that the two pathological processes can be easily differentiated, they give as one of the points of differentiation the widespread outlying distribution of the lesions of periarteritis nodosa and the close relationship of the rheumatic lesions to the cardiac area. Middleton and McCarter (1935) have also referred to this association in the two hundred cases reviewed by them.

Coates and Coombs (1923) called attention to the widespread distribution of the rheumatic nodule, its formation round a central small vascular lesion and its identity in all respects with the Aschoff node of the heart muscle and elsewhere. Bernard Shaw (1929) reported his post-mortem findings in a girl fifteen years of age whose death had been caused by acute rheumatic fever and showed widespread distribution of the rheumatic lesions, these being found in the carotids, subclavian and renal arteries, superior vena cava and in the muscles, and especially in and about their junction with the tendons. No lesions, however, were found in the vessels of the liver, kidneys, spleen, and lungs. Frazer (1934) also draws attention to the widespread nature of the rheumatic lesions and specially refers to the frequency of coronary endarteritis in acute rheumatism.

Notwithstanding the evidence that the lesions of acute rheumatism are undoubtedly widespread, there can be little doubt that the two types of vascular lesions are different and can be distinguished macroscopically and microscopically.

Von Glahn and Pappenheimer (1926), from a study of forty-seven consecutive cases of rheumatic heart disease, found in ten of the cases widespread rheumatic vascular lesions involving arteries of the lungs, aortic valve, kidney, ovary, testis, pancreas and perirenal and periadrenal adipose tissue. In two of the cases the pulmonary arteries and those of the kidney were extensively damaged. Their microscopic study revealed thickening of the vessels with reduction of the lumen and with a complete absence of thrombosis. They describe a fibrinous infiltration of the vessel usually limited by the internal elastic lamella, and necrosis of the cellular constituents of the vessel wall. External to these necrotic areas there was a distinctive cellular tissue composed of a loose fibrillar stroma partly fibrinous and containing nuclei and showing infiltration with scanty lymphoid and plasma cells, and occasional eosinophils, and a distinctive feature was the formation within this inflamed area of new blood channels. Von Glahn and Pappenheimer discuss the relationship of these lesions, which they considered to be typical of rheumatism, with those of periarteritis nodosa, and express the opinion that differentiation is possible and they summarize the distinguishing features as follows : (*a*) thrombosis is common in periarteritis nodosa and absent in the rheumatic lesions ; (*b*) periarteritis nodosa attacks arteries of medium calibre while those affected by rheumatism are usually of the small type and include the arterioles and sinusoidal capillaries ; (*c*) nodular formation in periarteritis nodosa is macroscopic as well as microscopic, while in rheumatism there is no nodular vascular develop-

ment and the lesions are invariably microscopic ; (*d*) there is absence of infarction, and haemorrhage from rupture in the rheumatic lesions ; and (*e*) conspicuous eosinophilic infiltration is present in most periarteritis nodosa lesions while in the rheumatic lesion eosinophilia is minimal.

Clinically there can be no doubt at all that the lesions of periarteritis nodosa produce results quite different from anything seen in a severe case of rheumatism. The arteritis is much more severe and profound and the development of gangrene, as in this case and particularly in the one reported by Barnard and Burbury (1934), should be sufficient in itself to show that the pathological process is on quite a different scale from that of acute rheumatism, in which the vascular lesions are not associated with thrombus formation ; nor is it possible that the lesions of periarteritis nodosa may sometimes simulate those of acute rheumatism, because in cases in which the association has been reported the typical Aschoff node has been found in close proximity to the typical lesions of periarteritis nodosa.

The microscopic appearance of the periarteritis nodosa lesion has been referred to by many observers. The media seems to be the part of the arterial wall which bears the brunt of initial damage, and at this point fibrinous degeneration and actual necrosis of the muscle takes place with damage to the elastica followed by massive infiltration of the adventitia with polymorphs, lymphocytes, plasma cells and, in some cases, eosinophils. This primary damage to the media leads to proliferation of the intima, and this produces occlusion, thrombosis and sometimes destruction which finally may result in haemorrhage or aneurysmal formation, and in some cases the local vascular occlusion is sufficiently severe and concentrated to produce local gangrene. The presence of eosinophils in the neighbourhood of an arterial lesion has been drawn attention to by several reporters (Barnard and Burbury, Rothstein and Welt, Middleton and McCarter, Friedberg and Gross), and it has been suggested that the eosinophilic involvement is an evidence of an allergic factor, and possibly it is here that the relationship of rheumatism and periarteritis nodosa exists. It is possible that a primary rheumatic infection in certain cases acts as the sensitizing factor and prepares the way for the destructive attack by the infective agent of periarteritis nodosa.

If it is agreed that syphilis is not an etiological factor and that the lesions of rheumatism and periarteritis nodosa are distinguishable both in early appearance and final results, it is difficult to suggest any other known infective agent which could account for an arteritis of so destructive a grade, and it is for this reason that some observers have claimed for this disease a specific etiological agent and probably a filtrable virus. Von Haum (1919) and Harris and Friedricks (1922) claim to have produced typical lesions, the former in guinea-pigs and the latter in rabbits, by inoculation of filtrates made from typical nodules taken at post-mortem. Ophüls criticizes this evidence, which he submits is unconvincing. He believes that the vascular damage may quite likely be produced by different agents under suitable conditions, and it would seem that he is of the opinion that the rheumatic infection, which he agrees is often associated with that of periarteritis nodosa, prepares the way for the latter, and

no doubt Ophüls' conception of the disease is that of an allergic manifestation. Carling and Hicks (1923) tried to repeat these animal experiments, but failed to introduce the disease into guinea-pigs. Gruber (1926) is of the opinion that they are not specific lesions and may be produced by several agents. Spiro (1919) believes that the lesions differ only quantitatively from those encountered in many infective diseases, e.g. measles, scarlatina, diphtheria.

The duration of the illness in twenty-three children, with one exception, was less than a year, and the majority died within six months of the onset (Rothstein and Welt). Lindberg (1931) reported a case in which the child, aged fifteen years, recovered after an illness of four-and-a-half years' duration. The circumstances of this illness resemble those of this patient.

Half the patients were adults of from thirty to fifty years of age and the ages in a series of one hundred and ninety-five ranged from nine months to seventy-eight years (Rothstein and Welt).

The main clinical features of the twenty-three children in the cases reported by Rothstein and Welt, in their order of approximate frequency were : pyrexia (17), increased pulse rate (12), abdominal pain (12), leucocytosis (12), prostration and weakness (11), muscle and joint pains (9), convulsions (11), skin rashes (8), oedema (8), anaemia (8), increased blood pressure (7), sore throat (6), and in only one case were there any subcutaneous nodules (Lindberg). In only two cases in addition to that under discussion was the diagnosis made by biopsy (Lindberg and Rothstein and Welt).

Three further instances of the disease in children have been described since 1933. That of Barnard and Burby (1934) was notable on account of the severity of the vascular lesions resulting in extensive gangrene of the limbs.

Friedberg and Gross (1934) reported a case, a child ten years old, but it is open to question if this was not an instance of acute rheumatic carditis with widespread vascular lesions. In the case reported by Krahulik, Rosenthal and Loughlin (1935) the child had superficial lesions of the ankle and the illness terminated fatally. The post-mortem picture was that of a healed rheumatic endocarditis, with fluid in the serous cavities and extensive vascular lesions in kidney, liver and spleen. No Aschoff nodes were present.

The superficial manifestations of the disease appear less common than those involving the organs and deeper structures. These skin lesions show considerable variation from case to case. The nodal erythema in this patient is thought a characteristic superficial manifestation of the disease ; the child described by Barnard and Burbury had no nodal erythema, but developed an increasing cyanosis and gangrene of the extremities. Debré and others (1928) refer to skin lesions consisting of polymorph-papulo-vesicular eruption of dark red-violet papules and vesicles with sero-haemorrhagic contents and patchy ecchymosis of limbs, mouth and nares, and also they mention erythematous rashes, trophic ulcers, subcutaneous nodules, petechiae, yet in none of these patients were the skin lesions dominant, nor were they the only manifestation of the disease.

In reviewing the numerous cases which have been reported in the literature

the impression that is produced is one of reasonable doubt as to how far it may be accepted that these arterial lesions constitute a single disease entity called periarteritis nodosa. This doubt especially arises, in some of those cases in which the acute rheumatic lesions has been reported to be associated with the lesion of periarteritis nodosa. In this country no such association has, so far as is known, been reported. On the other hand Bernard Shaw and Fraser have drawn attention to the widespread distribution of the rheumatic vascular lesion in the acute cases, and much therefore will depend upon the microscopic interpretation of the lesions present.

The point of differentiation summarized by Von Glahn and Pappenheimer, notably the presence or absence of thrombosis, are important, but possibly not conclusive. There can be, of course, no doubt at all that in the unequivocal cases of periarteritis nodosa, as for example that of Barnard and Burbury, there was a degree of arterial damage quite unlike anything seen in rheumatism and produced by some agent whose destructive action is unlike, certainly in its intensity, any other known metabolic or infective agent. The decision as to whether this destructive agent is a specific one, or whether given the suitable conditions, an arteritis of such magnitude can result from sensitization and allergic reaction by the inter-action of various agents must be left to the future to decide, and it is because of these interesting problems that arise in connection with this disease that this patient has been described.

Thanks are due to Dr. Cyril Polson, Pathologist at St. James' Hospital, for the pathological and blood reports and for the micro-photographs, and also for his interest in the case, and to Dr. E. C. Benn, Medical Superintendent at Seacroft Hospital, for allowing access to the notes ; and to Dr. Hester Woodcock, who drew attention to the unusual course of the illness whilst the child was under her care at Seacroft and who made detailed notes of the case.

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CONGENITAL STEATORRHOEA DUE TO PANCREATIC DEFECT

BY

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The cases of congenital steatorrhoea reported in the literature are few. It is therefore of interest to present eight cases with the results of post-mortem examination in four. Two other cases have been previously reported (Harper, 1930). The symptoms common to all these babies were failure to thrive on a normal diet, even on breast milk, and the peculiarity of their stools. These were bulky, frequent and offensive, with a rancid odour and of a pale creamy or pale green colour. In most of the cases oily material was passed with the stool and separately. As the children became older, x-ray examination of the bones showed osteoporosis, teeth were badly developed, anaemia became evident, sometimes of the macrocytic type, and there was great susceptibility to respiratory infections.

Case records

The histories of the eight cases reported here are as follows :

Case 1. E. L., a female infant, was first seen at the age of ten weeks. The only other child of the family was a healthy boy five years old. The mother stated that the pregnancy and confinement were normal. The family history was good. The baby's birth weight was 5¾ lb. Her weight at ten weeks was 7½ lb. and her height 19½ inches. The history was that the baby had had frequent green motions from birth, sometimes as many as fourteen, usually seven to eight daily. The motions were large and offensive. A stool seen at the consultation was pale, greenish yellow, with a rancid odour. The baby was breast fed and gained from 2 to 4 oz. a week. The appearance of the baby, the history and the appearance of the stool led to a provisional diagnosis of congenital pancreatic steatorrhoea being made. The breast feedings were supplemented with a dried separated milk. Reports from her doctor indicated that on the diet with a smaller amount of fat, her motions became less frequent, being reduced to two daily, and she continued to gain weight slowly. When the child began to use a chamber her mother noticed that oily material was passed with the stool. She was seen again at the age of two years and six months. The report from her doctor said that at six months of age she developed otitis media, which persisted for two years. She then had her tonsils and adenoids removed. A few days after the operation she had pyelitis. At this time her weight was 16 lb. 2 oz. and her height 30¾ inches. Her fontanelle was closed. Her teeth were almost entirely devoid of enamel.

She was admitted to the Royal Alexandra Hospital for Children. During her stay the following investigations were made :

1. The glucose tolerance test showed an approximately normal curve, on a slightly high level. Before glucose was given the blood sugar was 90 mgm. per 100 c.c.

½	hour	after	171	mgm. per cent.	
1	,,	,,	185	,,	,, ,,
1½	hours	,,	152	,,	,, ,,
2	,,	,,	102	,,	,, ,,

The urine was sugar free.

2. The serum calcium was 8·6 mgm. per 100 c.c.
   The serum phosphorus was 6 mgm. per 100 c.c.
3. Whole blood cholesterol was 80 mgm. per 100 c.c.
4. The Wassermann test was negative.
5. X-ray examination of the long bones showed osteoporosis which a later x-ray showed to be more marked.
6. The blood-count showed a marked anaemia with high colour index and many large red cells.

   RED BLOOD CELLS, 2,330,000 per c.mm. Haemoglobin, 48 per cent. Colour index, 1. There were numerous large red cells.

   WHITE CORPUSCLES, 7,200 per c.mm.

Polymorphs	74 per cent.	5,328 per c.mm.
Lymphocytes	23 ,, ,,	1,656 ,, ,,
Monocytes	3 ,, ,,	216 ,, ,,

   No abnormal white cells were seen.

7. The urine contained pus cells and Bacillus coli.
8. The examination of the stools gave the following results :

   The weight of dried faeces of twenty-four hour specimen was 96 gm. Faeces were pale, greasy and bulky, with rancid odour. Of the dried faeces 24 per cent. by weight was fat. Of the faecal fat 35 per cent. by weight was split, 65 per cent. was unsplit. In twenty-four hours the child excreted 23·4 gm. of total fat, of which 15 gm. were neutral fat.

During the early part of the child's stay in hospital her appetite was extremely bad. She was then given injections of insulin before her meals with a marked improvement. She gained weight well, her weight rising from 15 lb. to 19 lb. in just over a month. Her stools remained the same and her pyelitis did not clear up. The honorary urologist, Dr. Laidley, reported definite urethral obstruction. The bladder wall was hypertrophied. The ureteral orifices were patent and the ureters catheterized without obstruction. Dilatation of the urethra was advised and carried out. The gain in weight was not maintained and the child was taken home to return for further dilatation of the urethra. On discharge her weight was 17 lb. 6 oz. and on re-admission six months later it was 16½ lb. At this time the Pirquet test was positive and the urine from the right kidney showed the presence of tubercle bacilli. There were advanced changes in the lungs and the child died at the age of three years and four months, after a profuse haemorrhage from the bowel, of a generalized tuberculous infection.

The post-mortem examination was carried out and Dr. Tidswell, Director of the Department of Pathology, kindly supplied the following report :

' An emaciated, undersized child with tuberculous lesions in lungs (nodular

and diffuse, caseous and necrotic with secondary sepsis), spleen, both kidneys, intestines, mesenteric glands and in pancreatic lymph gland. The liver was bright yellow in colour and greasy. Microscopically there were fatty changes, involving all zones of the lobule, but least near the portal areas, most likely consequent on the toxic effect of the tuberculosis. The pancreas was large and looked like a mass of fat, nothing being seen resembling normal pancreas. Microscopically, the whole acinar tissue had disappeared (fig. 1), except for a few remnants of tubules near islets, which themselves, though conspicuous in their isolation, were few and scattered but of essentially normal character. The fatty tissue was of the ordinary type ; large clear sacs with a thin cell membrane and a marginal crescentic nucleus. In places some less mature cells showing various degrees of fat accumulation, representing stages of fat formation in connective tissue cells. There was no fibrosis. The appearances suggested fatty replacement of atrophied or undeveloped pancreatic tissue.'

Case 2. L. S., female, was under observation from the second day of life. The mother was unmarried and died from post-partum haemorrhage. The

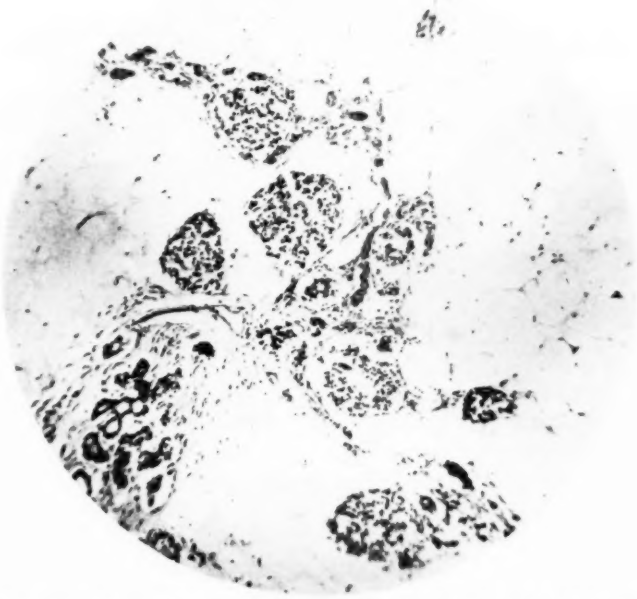

FIG. 1.—Pancreas of case 1, showing islets of Langerhans and scanty acinar cells. Pancreas made up mostly of fatty tissue.

baby was a small, apparently healthy child. Her weight when one day old was 5 lb. 4 oz. She failed to gain in weight when taking 60 calories per lb. body weight of breast milk. Her stools after meconium had been passed were pale green or pale creamy yellow with an offensive rancid odour. The stools were frequent—from five to ten daily—and some were unusually large. The total amount of faeces passed in the twenty-four hours was considerably larger than normal. The greasy, pale, offensive and large stools and the failure to gain in weight suggested that the baby might be suffering from a congenital pancreatic lesion. When she was a month old, a specimen of her faeces was examined at the Royal Alexandra Hospital for Children. The report was as follows : ' Fatty greenish stool—biliverdin present. Microscopically numerous fat

globules were seen, but no soap plaques. Total fat was 59 per cent. of the dried faeces. Of the total fat 82 per cent. was unsplit.'

After this examination was made the baby was given separated milk acidified with lactic acid with the addition of carbohydrate in the form of corn-cob syrup. At this time she weighed 4 lb. 12½ oz. She was given 57 calories per lb. body weight and on this food she made her first gain. She weighed 6 lb. when she was two months old. The stools retained their pale greenish yellow colour but diminished in size and number. When she was two-and-a-half months old, she developed broncho-pneumonia and died in the Royal Alexandra Hospital for Children. At the post-mortem examination the liver was found to be normal in appearance. Microscopically, there was patchy distribution of fatty infiltration. There were areas of haemopoiesis. The pancreas was rather small, weighing 2 gm. Dr. Tidswell's examination of sections from the

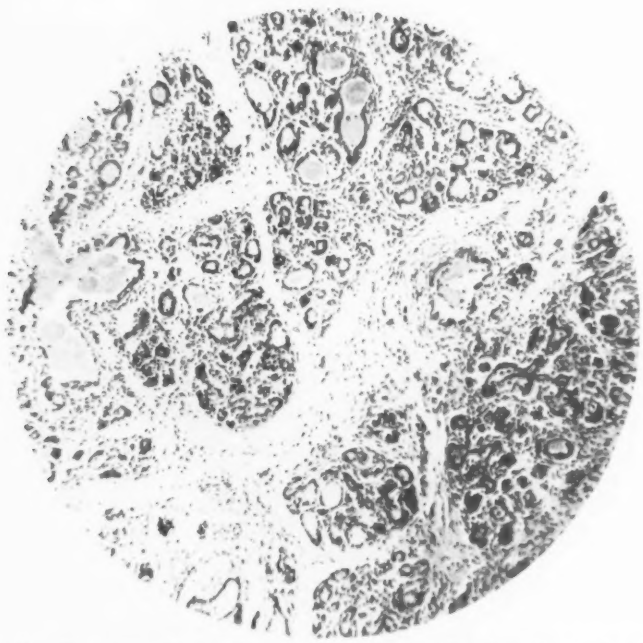

FIG. 2.—Pancreas of case 2, showing fibrosis of trabeculae and acini.

pancreas showed that ' the acinar cells are small and flat for the most part and destitute of a clear inner zone. The ducts are distended but not much distorted and contain some albuminous material. In the smaller ducts the lining cells are flattened, but become cuboidal and definitely columnar in the larger ducts. The islets are small but of normal appearance. The stroma is increased by well-formed fibrous tissue (fig. 2) showing collagenous fibres and fibroblasts and contains a fair sprinkling of macrophage (endotheloid) cells. There are no inflammatory areas. The increased fibrous tissue is chiefly intralobular. The interlobular tissue, though greater than normal, is relatively less abundant. The indications are of immaturity, affecting primarily or particularly the acinar cells with compensatory fibrosis most conspicuous in the alveolar stroma.'

Case 3. C. M., female, was admitted to the Royal Alexandra Hospital for Children from another institution, where she had been for two months without gaining in weight satisfactorily. She was aged five months on admission. She was the third child in the family. The first was healthy and the second had died

in the hospital at the age of ten days from ' collapse of the bowel.' The baby had been breast fed for two months, then on a modified dried milk. For the last two months she had been fed on fresh cow's milk modified with a fat emulsion and sugar with the addition of fifteen drops of cod-liver oil daily. The motions were reported to have been oily and offensive. No history was obtainable of the number of motions nor the amount of faeces passed. On admission, the stool was examined. The total fat was 59 per cent. of the dried faeces and of this fat 96·7 per cent. was split. The baby gained weight slowly on lactic acid milk made with whole milk for three weeks. She then developed broncho-pneumonia and died. At the post-mortem examination, apart from the broncho-pneumonia, the only other abnormalities were found in the liver and pancreas. The liver was pale and contained much fat. Microscopically there was marked generalized fatty infiltration. No necrosis nor fibrosis was present. The pancreas weighed 9 gm. and appeared normal to the naked eye. Dr. Tidswell's description of the sections from the pancreas is as follows : ' The acini are small and distorted, the cells shrunken and lacking the characteristic clear border. The ducts are distended and distorted into bizarre shapes. The epithelial cells are flattened and many are shed into the lumen. Most of the ducts show some structureless content, apparently albuminous. The islets are small, but essentially normal in character and arrangement, with wide tortuous capillaries. The interstitial tissue is markedly increased, widely separating the acini from one another and forming broad bands round the ducts and blood-vessels. Its cells generally are the usual histiocytes and although absolutely abundant are not increased in proportion to the excess of tissue. But here and there, without regular relationship to ducts or vessels, are masses of reticulo-endothelial cells, a few of which are multinuclear. There are no polymorph cells. In this tissue also can be seen lines of parallel flat cells apparently representing intercalary ducts. Collagen fibres are not marked ; the ground substance is hyaline rather than fibrillar. The vessels are congested but show no intimal changes. Whilst it is to be presumed that there has been immaturity of the gland substance followed by fibroid hyperplasia, there are signs that some degeneration is in progress.'

Case 4. D. S., female, was first seen at the age of eight-and-a-half months. Her birth weight was 7½ lb. and at eight-and-a-half months it was 11 lb. 15 oz. She had never done well and had been given many different foods with no improvement. She had bulky, pale and offensive stools with oily material passed with the stool and separately. She had sometimes as many as six in the day. She was given a low-fat diet and gained weight, but she was subject to attacks of bronchitis. She died at the age of thirteen months of broncho-pneumonia on June 23, 1933. An examination of her stool was carried out in January, 1933. Microscopically there were many neutral fat globules. The total fat was 40·8 per cent. of dried faeces, of which 88 per cent. was split. This examination was carried out when she was on her low-fat diet and probably there was little of the oily material in the specimen.

At the post-mortem examination, apart from the lungs, the only abnormality was found in the pancreas, which weighed 12 gm. and was nodular in appearance. Dr. Tidswell reports of the sections of the pancreas : ' The acini are few and widely separated by stroma. Acinar cells are essentially normal—columnar with a clear inner zone bordering a well-defined channel. The ducts are not manifestly dilated and their epithelium is of the normal columnar shape. The islets are conspicuous, sometimes large and of normal structure. Although the stroma is superabundant, it does not form bands and it is not restricted to the alveoli, but it is generally and rather evenly present throughout the gland. Its matrix is more hyaline than fibrous. There are numerous endo-

thelial cells as well as fibroblasts, and everywhere there is a permeation by cells of lymphoid type, occasionally showing plasmoid features. The suggestion conveyed by the appearances is of immaturity, as in the other cases.'

Case 5. M. O., female, was the second child. The first baby died at twelve days old from an infection of the mouth. The patient's birth weight was 8¼ lb. When first seen at the age of four-and-a-half months the weight was 7 lb. 7 oz. The baby was breast fed until one month old. Then she had a complement of fresh cow's milk modified with the addition of sugar of milk and water. She was weaned from the breast entirely at the age of six weeks and given a modified dried milk. The baby had irregular gains in weight. The stools were green and offensive and vomiting was frequent. She was admitted to an institution, where she remained for six weeks, losing weight all the time. When she came under observation she was below her birth weight, dehydrated and frail. Her stools were pale green or creamy yellow, bulky and rancid in odour. Oil was passed with and apart from the faeces. Her urine occasionally contained a small amount of sugar. She was given 10 oz. of breast milk and 20 oz. of a malted milk. In spite of taking over 70 calories per lb. body weight she only gained 1 oz. in a week and remained dehydrated. Her fasting blood sugar was 120 mgm. per 100 c.c. She was then given injections of insulin twice daily, and on the same amount of food she began to gain 1 oz. a day. Her weight rose to 9 lb. 6 oz., when she developed broncho-pneumonia and died.

The report on the examination of the stools at the Royal Alexandra Hospital for Children was as follows : Total fat, 47 gm. per 100 gm. of dried faeces. Of this fat 63 per cent. was unsplit. The stool examined consisted of liquid oil and large bulky air-containing residue, coloured pale green.

BLOOD COUNT.

Red blood corpuscles, 2,640,000 per c.mm. Hb., 50 per cent.
C.I., 0·9. White cell count, 18,800 per c.mm.

Polymorphs	80 per cent.	15,040 per c.mm.
Lymphocytes	15 ,, ,,	2,820 ,, ,,
Monocytes	5 ,, ,,	940 ,, ,,

Unfortunately no post-mortem examination was permitted. This patient was the only one of the series who had glycosuria at intervals.

Case 6. B. C., male, was the first child of young and healthy parents. He was first seen at the age of three months because he was vomiting. He was breast fed and gained 13½ oz. in two weeks and then lost weight. With regulation of the feeding the vomiting ceased, but the passage of large offensive motions was reported. The microscopic examination of the stool showed that it consisted largely of minute fat globules. The total fat of the dried faeces was 45·4 per cent. and in one specimen 60 per cent. of the fat was unsplit and in another 41 per cent. was unsplit. For a while the baby did well and gained weight on a fat-free diet. He then developed pneumonia and died at the age of eight months. No post-mortem examination was obtained.

Case 7. T. P., male, was first seen at the age of seven-and-a-half months. He was the second child, the first having died of pneumonia in his first year. He was breast fed until the eighth month. For his first three months he did well and gained weight. Then he began to fail and a nurse immediately noticed that oil was passed with his stool and apart from it. The stools were bulky and offensive. He was given a fat-free diet, but suffered from frequent attacks of bronchitis and he twice had pneumonia. His stools continued to be large and offensive. He died at the age of four-and-a-half years of broncho-

pneumonia. The first examination of his stool showed that the total fat content of the dried faeces was 71 per cent. and of this fat 39·5 per cent. was unsplit. On another occasion the report was that there were numerous fat globules present and few fatty acid crystals or soap plaques. The total fat was 54 per cent. of the dried faeces, and of this fat 51 per cent. was unsplit. No post-mortem examination was obtained.

Case 8. B. W., male, was the first child of his parents. The mother had an operation early in her pregnancy for retroversion of the uterus and at the

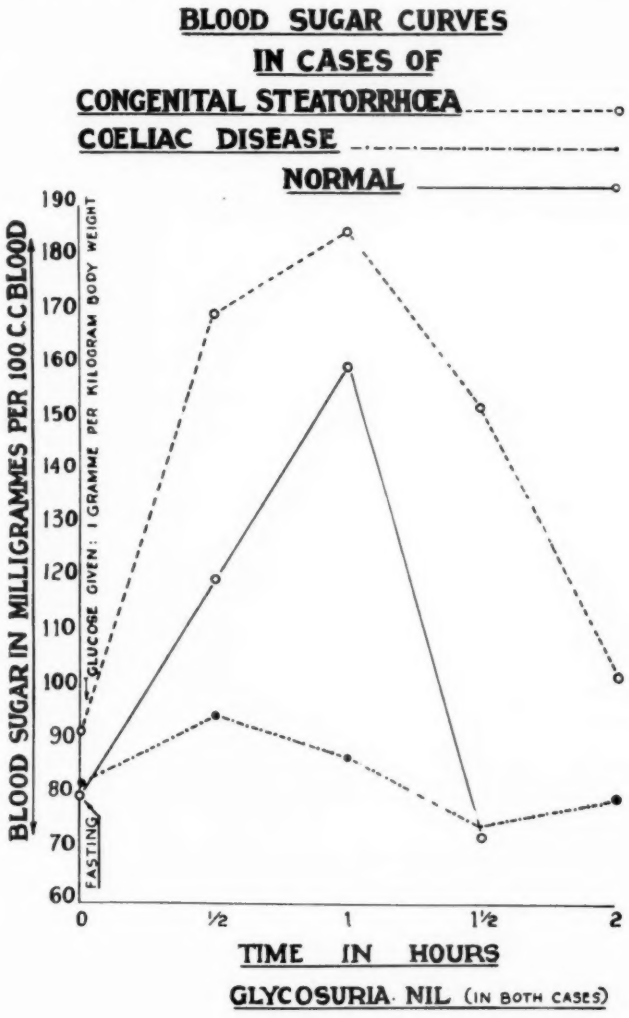

FIG. 3.

same time her appendix was removed. Otherwise the pregnancy and confinement were normal. The baby's birth weight was 7¾ lb. and at the age of six weeks he weighed 6¾ lb. He was partly breast fed for three months and then artificially fed. He was first seen at the age of five months. He had never thrived and always passed large, offensive, pale green stools. From the time he was five weeks old, his mother had noticed that there was oil in his stools. He had been under medical care and was given a dried milk made up to the

strength of whole cow's milk, egg yolk and biscuit. While on this diet, he vomited and had frequent, large, pale green stools which were rancid in odour. Oil was passed with the stool and between the passing of the motions. The number was usually six a day. He persistently lost weight. He was a thin, starved-looking baby, quite cheerful in appearance. A provisional diagnosis of congenital steatorrhoea was made and he was given a dried butter-milk. While on this food an examination of his stools gave a normal result with the fat well split. On the introduction of whole milk into his diet his stools again became oily. A second examination of his stool was made, this time at the Royal Alexandra Hospital for Children, with the following result : ' Numerous fat globules were seen under the microscope. The total fat was 44 per cent. of dried faeces. The unsplit fat was 59 per cent. of the faecal fat.' The baby was then given separated milk made with a pancreatized starch preparation and was also given a special malt extract. He is at the moment of writing aged twelve months and is gaining weight well, and his stools, although still large and offensive, are a more normal colour and he is not passing oil.*

TABLE I

FAT CONTENT IN STOOLS

CASE	PERCENTAGE OF TOTAL FAT IN DRIED FAECES	PERCENTAGE OF TOTAL FAT		APPEARANCE OF STOOL
		SPLIT	UNSPLIT	
1. E. L. ..	24	35	65	Butter-stool with bulky pale green and rancid faeces.
2. L. S. ..	59	18	82	Butter-stool with bulky pale green or creamy rancid stool.
3. C. W. ..	59	96·7	3·3	Pale fatty and bulky stool.
4. D. S. ..	40·8	88	12	Butter-stool with bulky rancid, pale yellow stool.
5. M. O. ..	47·1	37	63	Butter-stool—bulky pale cream and rancid stool.
6. B. C. ..	(*a*) 45·4 (*b*) 71	(*a*) 40 (*b*) 59	(*a*) 60 (*b*) 41	These examinations were made on the stools collected on two following days. Faeces bulky, lustrous and rancid in odour.
7. T. P. ..	53	49	51	Butter-stool with bulky pale green and rancid stool.
8. B. W. ..	44	41	59	Butter-stool with bulky pale creamy stool.

* Since writing this article, B. W. has died at the age of three years. He died from broncho-pneumonia after a prolonged illness. A post-mortem examination was done at the Royal Prince Alfred Hospital. The pancreas appears small and feels nodular. On close inspection numerous semi-transparent cysts of about pin-head size may be seen on the surface. On section the pancreas showed marked atrophy of the acini, with dilatation of the ducts. The islets of Langerhans are relatively normal.

Comment

The differences between coeliac disease and congenital steatorrhoea are given in the following table (see also fig. 3) :

CONGENITAL PANCREATIC STEATORRHOEA	COELIAC DISEASE
Symptoms present from birth.	Age of onset, nine months to two years.
Oil is present in the stools (butter-stools).	Oil is not present.
High faecal fat with large amount of unsplit fat.	High faecal fat, well split.
Glucose tolerance curve on the high side of normal.	Glucose tolerance curve flat.
Post-mortem lesions of the pancreas are found.	Post-mortem examination shows no lesions of the pancreas.

The signs due to the failure to absorb fat are common to both conditions—such as emaciation, meteorism, anaemia and osteoporosis.

R. Miller (1922–23) clearly defines the various types of fatty stools. He says :

' Thus we see that there are three types of fatty stool. First, the type of pancreatic insufficiency with a large excess of fat in the stools, chiefly in the form of neutral fat. This condition never occurs in coeliac disease. Secondly, that of excess fat chiefly in the form of fatty acids giving the classical coeliac stools, large, pale, unformed and very offensive. Thirdly, there is the soapy stool, looking normal on casual inspection. It is not offensive and not frequent, yet it may be found to contain anything up to 50 per cent. of fat, chiefly in the form of soaps.'

The patients reported here all gained weight and improved in their general physical condition when they were given a diet containing a considerable amount of protein and carbohydrate and no fat. They were all given a larger number of calories per pound body weight than the number of calories on which babies gain and develop normally. Even after the fat was cut out of their diet, the stools remained larger than normal, although they diminished in frequency. This suggests that the babies were still losing a considerable amount of the food ingested.

H. Morley Fletcher (1934) says : ' Of the three important ferments normally present in the secretion (of the pancreas), it would seem that, particularly in children, the lipase steapsin is the one most liable to show variations in its functional activity as the result of disease of the pancreas. Disturbance of this function of the gland leads to the presence of abnormal quantities of neutral fat in the faeces, giving rise to the so-called " fatty stools," or " steatorrhoea," as it is termed by some authors. It is advisable to restrict the use of the name " steatorrhoea " to the passage of liquid fat with the stools. A congenital form of this condition has been described. The proteolytic ferment trypsin is less commonly affected in pancreatic disease.'

In case 3 and case 4 the fat in the specimen of faeces examined was well split. In both cases only one specimen was examined. In one ' butter-stools ' were present ; in the other they were not noted.

Thaysen (1932) states that in the case of pancreatogenous fatty diarrhoea the so-called ' butter-stool ' is usually present, but it was absent in two of his six cases. He also says : ' That the greatest part of the fat in the faeces is found in the form of split products (free fatty acids and soaps) is no proof of a normal function of the pancreas, as the same is found even to a higher degree in the pancreatogenous fatty diarrhoea.'

In the analysis of the faecal fat in seven cases of undoubted pancreatic disease, Pratt (1912) found that there was an increase of neutral fat in four.

In the diagnosis of fatty diarrhoea due to pancreatic defect, Thaysen regards the elimination of nitrogen and the glucose tolerance curve as of greater importance than the chemical estimation of the fat content of the faeces. Unfortunately in these cases there was no opportunity for the estimation of the elimination of nitrogen.

As Garrod (1923) says : ' The pancreas, like other glands, is subject to a great variety of lesions, and it is not surprising that in cases of disease of this gland the amounts and proportions of the fatty substances excreted vary widely.'

The cases reported by Clarke and Hadfield (1924), by Burghard (1925), Passini (1919), and Gross (1926) are all similar to those reported here. Julius Hess and Saphir (1935) have recently reported three cases which they call ' coeliac disease.'

In these cases, although the clinical condition is not reported fully, the symptoms were present from birth and in two of them there was a large amount of neutral fat present in the stools. All these died of broncho-pneumonia at the ages of eighteen months, nine months and three years respectively. At the post-mortem examination pancreatic disease was evident. Hess and Saphir say : ' Burghard's, Cross's and Passini's cases, which revealed severe changes in the pancreas, are regarded as examples of coeliac disease.'

This statement is surely incorrect, as they are reported by the authors as examples of disease of the pancreas. The cases of Hess and Saphir evidently also belong to the group of congenital steatorrhoea due to a lesion of the pancreas, and are not cases of coeliac disease.

A. McBryde (1935) reports the case of a child who had had ' symptoms characteristic of coeliac disease from the age of one month ' and who weighed 11 lb. at the age of twenty-seven months. This child had a hyperchromic megalocytic anaemia. It seems probable that this child also should be placed in this same group.

Clarke and Hadfield (1924) say in the report of their case : ' Several points in the history and physical condition suggested a diagnosis of coeliac disease, in itself an obscure complaint. This diagnosis, untenable on closer clinical observation, was definitely excluded by the post-mortem examination.'

Garrod and Hurtley (1913) reported cases of congenital steatorrhoea occurring in more than one member of a family in which there was no failure of nutrition or other evidence of pancreatic defect. Their patient, seen after an interval of seven years, was a well-grown lad of fifteen engaged in active work. Examination of his stools at this time showed that the anomaly still persisted.

Miller and Perkins (1920) reported an apparently similar case, but this patient died of broncho-pneumonia and no autopsy was permitted.

Cockayne (1933) reported a case of congenital steatorrhoea which he took to belong to the same group as Garrod and Hurtley's. The facts that the child weighed only 17 lb. at the age of a year and ten months and that she died at the age of two years and four months of broncho-pneumonia suggest the possibility that the steatorrhoea may have been due to a congenital pancreatic lesion similar to those reported here. There was no family history in Cockayne's case and two children born subsequently were normal. In the family reported by Soecknick and Thoenes (1927), mentioned by Cockayne, all three children had steatorrhoea. One died of broncho-pneumonia and another of hydrocephalus. Cockayne mentions the high mortality and the frequency with which broncho-pneumonia was the cause of death. He says that this frequency may be only a coincidence, but the fact that in eight out of ten of the writer's cases broncho-pneumonia was the cause of death and in the ninth generalized tuberculosis, seems to point to a greatly reduced resistance to respiratory infections in these cases. The cases reported by Miller and Perkins, by Hess and Saphir and by Burghard also all died of broncho-pneumonia.

In only one of the series of cases reported here was there more than one child in the family affected. The child, a boy, born subsequently to M. O., case 5, and who is now fifteen months old, is reported by his mother occasionally to pass butter-stools and the stools are always large, pale and offensive. On the only examination of his faeces which has been made, it was found that there was a high total fat present, namely 58 per cent. of the dried faeces was fat and this was well split. This child is at present under observation. Although he is underweight for his age and subject to attacks of bronchitis, he is doing fairly well on a low-fat diet with high protein and carbohydrate.

On reviewing the reported cases of congenital steatorrhoea, that of Garrod and Hurtley seems to be the only one which has attained to an age beyond that of early childhood and who appeared to be of normal physical development at the age of fifteen years. Garrod (1923) says of his case :

' It is tempting, but perhaps not justifiable, to connect this with an isolated failure of one single factor as distinguished from impairment or abolition of the pancreas as a whole.' He also says : ' It must be mentioned that steatorrhoea due to organic lesions of the pancreas may persist for years without grave impairment of the general health.' He mentions the remarkable case of a medical man who died at the age of ninety, having passed butter stools from his sixty-third year. At the autopsy his pancreatic duct was found to be blocked by calculi, and the gland substance was almost entirely replaced by fat.

The consideration of the histology of the pancreas in those cases in which an atutopsy was obtained suggests a failure of development of the gland. Burghard (1925) points out the difference between the histological appearances in those cases which occur in adults caused by obstruction to the excretory ducts and the dilatation and distortion of the ducts which were present in his case and in some of those reported here. He considers that this condition is a congenital one due to failure of normal development of the pancreas.

The conclusion arrived at after reviewing the material available in the literature and the cases reported here is that in cases in which there is evidence of

the passage of fatty stools from birth (particularly ' butter-stools ') with failure of nutrition, the diagnosis of a congenital defect of the pancreas can reasonably be made.

The author is greatly indebted to Frank Tidswell, M.D., Director of the Department of Pathology, Royal Alexandra Hospital for Children, Sydney, who has given help in discussing these cases and in examining and reporting on the sections; also to Phyllis Anderson, M.B., Ch.M., of the same department, for the examination of the stools and blood ; and to Superintendent of the Royal Prince Alfred Hospital for the report of a post-mortem examination.

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THE ADMINISTRATION OF THYROID GLAND TO PREMATURE BABIES

BY

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As far as can be ascertained from the literature, the administration of thyroid gland to premature babies was first suggested by Pritchard (1934). He then described its use in his book on ' The New Born Baby,' but he was certainly advocating this therapeutic measure long before this time. The underlying principle for this form of treatment is of much earlier date and goes back to the classical experiments of Gudernatsch (1913–14), on the feeding of tadpoles with thyroid gland to speed up their development into frogs. This pioneer's conclusions were as follows:

' The experiments of 1911 and 1912 leave no doubt that the mammalian thyroid contains an agens which, when given as food, calls forth a rapid differentiation in a developing vertebrate organism.'

The object of administering thyroid gland to the premature baby is to hasten maturation, so that the various essential functions, such as those of respiration, digestion and heat regulation, may be more expertly undertaken than in the immature state. It is differentiation of function and structure which is achieved in the tadpole, and not growth. In fact, the resulting frog will usually be undersized and its length of life is generally shorter than the average. In the premature baby the use of thyroid should be limited to such a period as seems necessary to improve functional development. The gland is not being used to supply a deficiency, but merely to act as a stimulant to remove the inertia which makes the premature baby so difficult to manage.

This point on the question of a possible deficiency of thyroid secretion in the premature baby must be elaborated briefly, for Collis (1936), in strongly supporting the use of thyroid for premature babies, has suggested that new-born babies do not in general secrete thyroxin in the first few weeks of life, implying that the premature baby may be handicapped on this account. Histological evidence (Murray, 1927) does not support this view. The thyroid gland in the full-term human foetus and in the newly born infant presents a normal colloid

state provided that careful precautions are taken to prevent degenerative changes in the course of preparing histological specimens. A biochemical study (Elmer and Scheps, 1935) indicates that the amount of thyroxin in the thyroid gland of the foetus and new-born baby is of the same order as in a normal adult. Aldrich (1936) has also pointed out that one of a set of twins may be a cretin, indicating that normally a foetus develops its own thyroid secretion is is not dependent upon a maternal supply. This author also emphasizes the fact that in general thyroid gland speeds up development rather than the promotion of growth or gain in weight.

These introductory considerations will be referred to again below in a discussion on the assessment of results. The main object of this communication is to set out such results, obtained in a controlled therapeutic trial at Queen Charlotte's Maternity Hospital between November 1935 and January 1937.

Method of investigation

It has been already pointed out (Moncrieff, 1936) in connexion with a similar investigation of the use of oestrin for premature babies that what may be termed ' contemporary controls ' are essential. So much depends upon the general management and nursing care, the ward, temperature, the feeding and the risks of infection that the value of any procedure for premature babies can only be judged if at the same time of year, in the same ward and looked after by the same nurses there are similar babies not submitted to the method of treatment or management under trial. At the same time it is important that so far as possible the nursing staff should be unaware of which babies are receiving special treatment, so that any bias may be absent from their views on the value of such treatment. In the present investigation this was achieved (at least at the onset) by the use of ' dummy ' thyroid tablets. The nursing staff, however, early in the investigation, was convinced that the thyroid-treated babies were easier to feed and manage, and since the thyroid tablets were slightly browner in colour than the dummy tablets, the nurses soon ceased to be unaware of which babies were treated and which were controls. This was to some extent unfortunate as possibly affecting the results. However, as will be shown below, the main point in favour of the use of thyroid gland for premature infants which emerges from this investigation is a lowering of the mortality rate, and this can scarcely be attributed to any decreased care of the control babies.

For the period mentioned above every baby of 5 lb. or under at birth came under the scheme. It would be out of place to argue here on the definition of prematurity and to what extent weight is a reliable guide. At Queen Charlotte's Hospital the weight standard has been in use for a long time, and it certainly serves as useful arbitrary measure. (In passing it may be remarked that the standard has now been raised to 5½ lb. in view of certain developments recorded in American and European literature.) There were during the period chosen one hundred and three such babies born alive. Of these forty-one were excluded from the experiment for the following reasons :

Thirty-two died shortly after birth or were very ill for several days (subsequently dying) or suffered from severe disease (hæmorrhagic disease) or from severe congenital malformation.

Nine were nearly 5 lb. in weight, not at all immature in function and treated as completely normal babies from the beginning.

With regard to this second group it should be explained that the arrangements at the hospital are such that each of three floors has a side ward in which small and ill infants are nursed. These nine infants never came into the side wards at all, being regarded as essentially small normal babies.

The remaining sixty-two babies came into the investigation ; all were identically treated as regards room temperature and humidity, general hygiene and feeding. Each baby was seen by the author as soon as possible after birth and at intervals during its stay in hospital. Breast milk was always used in the early days of life for all the premature babies, obtained at first from a ' pool ' of surplus milk and later, if possible, from the baby's mother. Weak milk mixtures (' humanized ' dried milk or peptonized milk mixtures) had to be introduced in some instances, but rarely before the end of the first week of life, and since the results here presented refer to the first two weeks of life only, it may be assumed that the qualitative feeding conditions were identical. It is, of course, fundamental to the problem that the quantities of milk were dependent largely on the baby's ability to suck and swallow. The stronger and more mature the baby the more feed would be taken, and it was to promote such strength and maturity that thyroid was being given.

Alternate babies received thyroid extract in lactose tablets or plain ' dummy ' tablets (all kindly supplied for the investigation by Messrs. Oxo Limited). Each tablet of thyroid extract contained 1/20 grain, and these were labelled ' thyroid A.' The lactose tablets were labelled ' thyroid B.' The dosage used was on a basis of 1/20 grain (i.e. one tablet) daily per lb. body weight. This was continued for at least a fortnight unless the baby was fit enough to leave hospital before this time. The tablets were crushed and given from a spoon with a little water. The dose chosen was more or less arbitrary. Pritchard (1934) has recommended 1/10 grain per lb. body weight daily as a maximum, and half this seemed a safe amount to employ. Careful records were kept of the temperature (rectal) night and morning and of the weight. Unless the baby was obviously unfit, daily weighing has been practised. With twins one received ' thyroid A ' and the other ' thyroid B.' This somewhat upset the ' alternative baby ' plan and in the end it was found that thirty-three babies had received ' thyroid A ' and twenty-nine ' thyroid B.' These numbers appeared near enough for comparison purposes.

The assessment of results

It is first necessary to discuss how the results may be assessed. As was remarked in connexion with the oestrin investigation (Moncrieff, 1936), when nursing skill is of a high standard the general mortality and morbidity rates are already so low that it is difficult to achieve improvement with any special form of treatment. Thus of the sixty-two babies who came into the investigation there were only seven deaths, and anyone with experience of managing premature babies will realize that a mortality of 11 per cent. is low. (Of the whole one hundred and three babies born alive during the period there were thirty-eight deaths. Deducting the seven deaths already mentioned, this means that thirty-one out of the thirty-two babies classified as being too

ill or weak for treatment died, most of them within forty-eight hours after delivery.) Despite this small number of deaths a point will be made later about the mortality rates, since there appeared to be a difference between the group receiving thyroid and the group which did not.

The question of gain in weight, used as the main test in the oestrin experiment, presents a great difficulty. Thyroid gland presumably stimulates metabolism and may promote a loss rather than a gain in weight. Nevertheless the 'stimulated' baby will probably take its feeds better than the 'unstimulated' baby (if thyroid is to have any effect) and thus a better gain might be expected. At any rate, it seems fair to assume that no very clear-cut results can be expected from the weight charts and any attempt to obtain such results by increasing the dosage of thyroid will produce the opposite effect. It may be remarked in passing that with the dose employed (1/20 grain per lb. body weight daily) no toxic symptoms were ever observed and there was no case of diarrhoea.

The temperature range has been considered for each baby, since it has been suggested by Pritchard that it was especially in the inert baby with subnormal temperature that good results were obtained. For the purpose of these results the records in the first forty-eight hours have been disregarded, since violent fluctuations may occur during this period. The highest and the lowest recorded temperatures in the subsequent stay in hospital has been taken for each baby and averaged for the group.

Analysis of results

The results can now be summarized in the form of a table (table 1).

TABLE 1

ALL 'TREATED' BABIES (62)

	NO. OF BABIES	AVERAGE WEIGHT AT BIRTH	AVERAGE WEIGHT 7TH DAY OF LIFE	PER CENT. DECREASE IN WEIGHT 7TH DAY	AVERAGE WEIGHT 14TH DAY	PER CENT. INCREASE OR DECREASE OVER BIRTH WEIGHT 14TH DAY	AVERAGE TEMPERATURE RANGE	DEATHS
Group A (received thyroid).	33	4 lb. 3 oz.	3 lb. 15 oz. (32 babies)	6	4lb. 0 oz. (21 babies)	− 4·5	96·5° F. –98·5°F.	2 ; 6 per cent.
Group B (no thyroid).	29	4 lb. 7 oz.	4 lb. 4 oz. (21 babies)	4·2	4 lb. 11 oz. (17 babies)	+ 5·6	97·1° F. –98·3° F.	5 ; 17 per cent.

Both groups consisted of babies whose estimated maturity lay between thirty-two weeks and term. The causes of the prematurity—toxaemia, antepartum haemorrhage, and multiple pregnancy—appeared to be the same in both groups. The lowest weight in both groups was 3 lb. 2 oz. It will be noticed in table 1 that only fifty-seven out of the sixty-two babies remained for comparison of weights on the seventh day. In group A one baby had already died (on the

second day of life) and in group B four babies had died (on the third, fourth, sixth and seventh day, respectively). Similarly by the fourteenth day the numbers had again been decreased. There had been one more death in each group and seventeen had been discharged from hospital, ten in group A (32 per cent. of survivors) and seven in group B (29 per cent. of survivors). Although this decreases the already small number of babies available for study, a separate analysis of the babies followed through to the fourteenth day is given below (table 2). It is obvious that the effect of deaths in both series is to remove those babies who were doing badly, and since there were two deaths in group A and five deaths in group B this gives a certain bias to the results in favour of group A. On the other hand the discharges of babies who were doing well—largely because the mothers were anxious to get home and only when the babies were well established on the breast or on mixed breast and complementary feeds—were about equal in the two groups.

TABLE 2
'SURVIVORS' (38)

	NO. OF BABIES	AVERAGE WEIGHT AT BIRTH	AVERAGE WEIGHT 14TH DAY OF LIFE	PER CENT. INCREASE OR DECREASE OVER BIRTH WEIGHT 14TH DAY
Group A (received thyroid).	21	4 lb. 1 oz.	4 lb. 1 oz.	− 1·5
Group B (no thyroid) ..	17	4 lb. 7 oz.	4 lb. 8 oz.	+ 1·8

Before proceeding to a discussion of the results in more detail, the weights at birth, seventh day and fourteenth day of four sets of twins are given in table 3.

TABLE 3
FOUR SETS OF TWINS

GROUP	BIRTH WEIGHT	7TH DAY WEIGHT	14TH DAY WEIGHT
A	4·14	4·12	5·3
B	4·5	4·8	4·11
A	4·3	4·0	4·3
B	4·8	4·4	4·8
A	3·15	3·4	3·15
B	4·10	4·6	4·7
A	3·11	3·6	3·5
B	4·11	3·13	Died

General discussion

It is proposed to consider the general results of thyroid administration under the headings of effects on weight, effects on temperature, mortality and sex differences. The last section is included because the present study must be regarded as a continuation of the work already mentioned in connexion with

the use of oestrin for premature babies, in which a sex difference appeared to be present.

Weight.—It has already been explained that any striking effect on the weight of the babies receiving thyroid was not to be expected, since its stimulating action on appetite and digestion might well be counterbalanced by its general raising of the metabolic rate, tending to produce a weight loss. In table 1 it will be seen that at the end of a week the percentage decrease in weight was similar in the treated and untreated groups, although slightly more in the former (6 per cent. and 4·2 per cent. respectively). By the end of fourteen days the untreated group appears to show a great advantage (a gain of 5·6 per cent. as compared with a loss of 4·5 per cent. in the treated group), but this may well be accounted for by the removal of certain unsatisfactory babies from the final figures, since in all there had been five deaths in this group and only two in the treated group. In fact, between the seventh and fourteenth day only one baby died in each group, but the final comparison is made between birth weight and fourteenth-day weight. The figures in table 2 tend to bear out this contention, since after removal by death or discharge of babies not available for comparison on the fourteenth day, the two groups show little difference in the weight. The twenty-one treated babies are on the average 1 oz. under birth weight and the seventeen untreated babies are 1 oz. over birth weight. Table 3, giving the results in four sets of twins, shows also little difference between the weights of the treated and untreated babies. In general the effect on weight may be summarized by the statement that thyroid administration in the dosage employed in this investigation (1/20 grain of thyroid extract per lb. of body weight daily) does not produce any obvious beneficial results on the weight curve.

It must, however, be borne in mind that the nursing available for the premature babies at Queen Charlotte's Hospital is of a high standard. The more permanent nursing staff have had extensive experience, and the skill displayed in getting small babies to take their feeds is great. Thyroid might have the effect in making this procedure easier for less experienced nurses. In the course of this investigation the opinion was frequently expressed by the nurses in charge that the ' treated ' babies were definitely easier to manage. In fact, as already mentioned, it soon became impossible to conceal that the ' dummy ' tablets labelled ' thyroid B ' did not contain any thyroid, for the babies receiving them were thought by the nursing staff to be more difficult to feed and to keep warm than those in group A receiving thyroid extract.

Temperature.—Rectal temperatures were taken night and morning for all the babies in the series. The records of the first two days of life have been neglected, since violent fluctuations may occur during this period. The highest and lowest average temperatures for each group of babies is given in table 1. The upper limits are similar and the lower limits appear to show a slight advantage in favour of the untreated group. All the premature babies here described are clothed in gamgee jackets, with separate gamgee coverings for the head, hands and feet in the smallest babies. In addition, electric pads of the ' Thermega ' pattern are placed over the bed-clothes in all premature babies. These pads allow of three grades of temperature, and they are con-

stantly adjusted by the nursing staff according to the temperatures of the babies, as well as by the results of observation. Although the untreated babies appeared to have a higher lowest level, on the average there was no doubt about the effect of thyroid in raising the temperature in some of the treated series (fig. 1), and here again the opinion of the nursing staff was emphatic that the thyroid-receiving babies are easier to keep warm.

Mortality.—It will be remembered that of the whole series of one hundred and three premature babies born alive at Queen Charlotte's Hospital during the period of the investigation, forty-one were excluded from the numbers accepted for 'treatment' and observation, thirty-two of whom died shortly

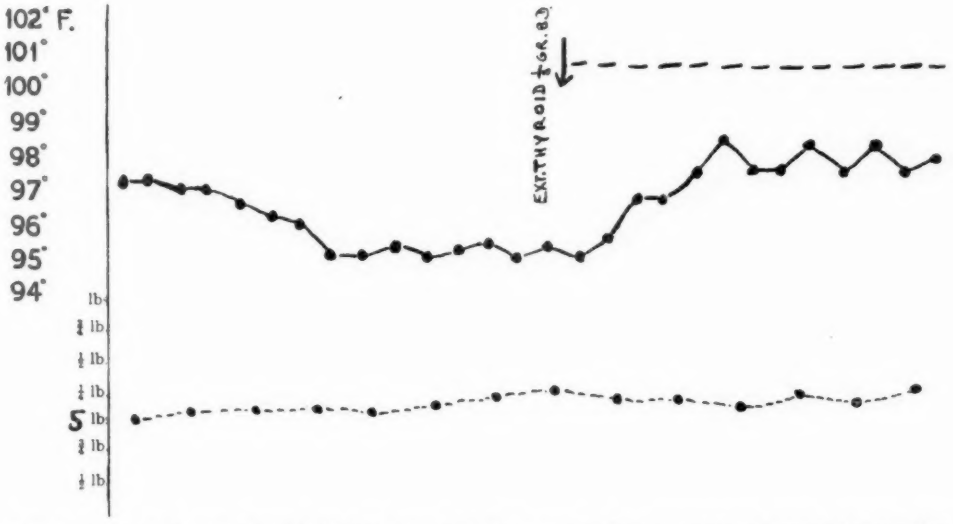

FIG. 1.—Effect of ext. thyroid (½ grain twice a day) upon the temperature curve (upper line) of a new-born baby weighing 5 lb. at birth. The lower dotted line shows the weight curve and there is a slight arrest in the upward curve when thyroid is begun. The records for the first three days have been omitted. The thyroid was given on the eleventh day of life because of the sub-normal temperature.

after birth or were very ill, suffering from some severe disease or congenital malformation. The sixty-two remaining for the purpose of the controlled experiment were, therefore, reasonably 'good starters.' Of those receiving thyroid two died and of those not receiving thyroid five died. In other words, the mortality rate of the selected babies was 6 per cent. in those receiving thyroid and 17 per cent. in those not receiving thyroid, nearly three times as high. Of the seven deaths, two, one in each group, occurred during the first forty-eight hours of life, so that the untreated group shows four deaths after this period as against one only in the treated group. One of the deaths in group B was in the larger of twins, the smaller, treated baby surviving. The figures are small, but since all other conditions as regards nursing care and feeding were identical and carried on by the same staff at the same period of time, the difference may be regarded as significant and, indeed, represents the main argument in favour of thyroid administration.

Sex differences.—In the oestrin-treated series previously reported (Moncrieff,

1936), thirty-three out of the total series of fifty-four babies were females, a curious sex preponderance. Further, the slight but definite improvement in the weight by the fourteenth day in the oestrin-treated series appeared to be mainly due to improvement effected in the female babies. Since a sex hormone was involved in the oestrin series such results may have some special significance. In the present series the thirty-eight babies followed through to the fourteenth day show a predominance of the male sex, the number of male babies being twenty-three and females fifteen. The present investigation followed immediately after the oestrin series, and the curious difference in the two series serves to emphasize the importance of large numbers of cases spread over a long period before altogether satisfactory results can be obtained. Analysing this group of thirty-eight babies according to sex shows approximately equal results for the males and females. In the thyroid-receiving group the males were 1 oz. under birth weight by the fourteenth day and the females had just recovered the birth weight. In the control group the males were 2 oz. over birth weight by the fourteenth day and the females were 2 oz. under birth weight. These observations have a more important bearing in retrospect on the oestrin series than upon the present investigation, since there is no evidence of any great difference in the two sexes when thyroid is used.

Conclusions

The administration of thyroid extract (1/20 grain per lb. body weight daily) to premature babies appears to exert a beneficial effect in speeding up maturation. In a controlled investigation the mortality rate in a group receiving thyroid was only one third that in the control group. Reasons are adduced why better gains in weight are not obtained, and the opinion of the nursing staff is mentioned as emphatically in favour of thyroid administration as rendering small babies easier to manage as regards feeding and keeping them warm.

Acknowledgements

Once again cordial thanks must be expressed to the nursing staff of Queen Charlotte's Hospital for their careful collaboration and their keen attention to the detailed recording of weights and temperatures required. Messrs. Oxo Limited, kindly supplied the specially prepared tablets of thyroid extract and the dummy tablets of lactose only. The author is also indebted to Dr. Eric Pritchard for his initial suggestions and continued interest.

The results here published were presented as an occasional paper before the Children's Section of the British Medical Association at the Belfast Meeting in July 1937. Permission to publish them here in a different form has been granted by the Editor of the British Medical Journal.

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UNDULANT FEVER IN CHILDREN

BY

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Since the discovery of the part played by the brucella abortus organisms in the production of undulant fever in man, increasing numbers of cases have been reported. In this country a series of three hundred cases has been recorded by Dalrymple Champneys (1936). This series agrees with all others published in that, first, it shows a great preponderance of cases amongst males—out of two hundred and fifty-five cases whose sex was known, one hundred and seventy were males and eighty-five females ; secondly, it emphasizes the comparative rarity of the condition amongst children, there being only twelve cases under ten years of age (Champneys, 1935). From Scotland, Beattie and his co-workers (1935) have reported ninety-seven cases collected between 1929 and 1934 ; five of these cases were below ten years and five between the ages of ten and twenty years.

This present paper is a study of eight cases seen, either in private or at the Hospital for Sick Children, Great Ormond Street, between the ages of six and fourteen-and-a-half years. Children comprise the largest milk-consuming section of the community, but the rarity of the disease among them has not yet been satisfactorily explained. It is probable that many cases are never recognized.

Clinical features

Of the eight cases the youngest was six years old, and only one was a girl. In every case the beginning of the illness was abrupt, with signs of an infection of the nasopharynx, and the diagnosis was either that of a common cold or of influenza ; it was only the persistence of the temperature which attracted attention. Sweating was a prominent feature in only two of the cases ; fatigue was marked in one case. None complained of headaches or joint-pains ; the appetite was not impaired. No case had a rigor. The temperature reached 104° F. in one case; more usually it ran an irregular course between 99° and 100·5° F. In four instances the bouts of fever recurred over a period of four months ; in one case they persisted for a year. One boy attended the out-patient department for a year with recurrent coughs and colds, and was only diagnosed as a case of undulant fever after his sister had been admitted to the

wards with the same disease. An enlarged spleen was found in one case otherwise the physical examination was negative.

Diagnosis

Agglutinations.—These were positive in every case to a titre of 1 in 500 or higher. Case 4 emphasizes the importance of carrying the agglutinations sufficiently far to detect a positive result in the presence of a pro-zone.

Skin tests.—Using 0·2 c.c. of a vaccine containing both abortus and melitensis organisms, skin tests were done on the patients, and gave in each case a strongly positive reaction. An attempt was made to use the test to discover possible latent cases of undulant fever among patients in the wards at Great Ormond Street. A preparation of brucellin containing both abortus and melitensis organisms was used : 0·1 c.c. of a 1 in 100 dilution was injected intracutaneously. A positive reaction, as given by a patient with the disease, was taken as an erythematous reaction about 1½ inch in diameter occurring around the site of the injection within twenty-four hours. Out of sixty cases investigated in this way, two gave such a reaction ; agglutination reactions were, however, entirely negative in both cases. It would appear therefore that the skin test by itself does not give reliable evidence of the disease.

Blood picture.—An anaemia with an absolute or relative lymphocytosis is mentioned by Dalrymple Champneys (1935) as the most usual finding. The blood count in two cases in this series gave such a picture, but one case had an increased number of both red and white cells.

Blood culture.—This examination was not performed upon any of the cases in this series.

Case Histories

CASE 1. Male, aged six years, was taken ill on August 1, 1934. Agglutinations against the brucella organisms on August 11 were negative. His temperature continued to keep up, and on October 22 his blood agglutinated b. abortus to a titre of 1 in 500 and b. melitensis to 1 in 200. Both skin tests were positive. A differential white cell count showed 30 per cent. polymorphs, 61 per cent. lymphocytes and 1 per cent. monocytes.

CASE 2. Male, aged fourteen-and-a-half years, was seen in March, 1934. He had been running a temperature up to 100° F. since the beginning of the year. His illness had appeared to start with a mild otitis. He had not vomited, but he had a marked anorexia. Physical examination showed nothing abnormal except for a furred tongue. An x-ray of his chest showed enlarged hilar glands. His temperature continued, but, apart from night-sweats, he appeared to be in excellent health. In December 1934, almost a year after the onset of the disease, his blood gave a strongly positive agglutination with b. melitensis.

CASE 3. Male, aged six-and-a-half years, came from Yorkshire. He began with a feverish cold in November 1934, and from then on his temperature continued between 99° and 100° F. On January 16, 1935, physical examination showed nothing abnormal. An x-ray of his chest showed enlarged hilar shadows. The undulant fever skin test was strongly positive. His blood agglutinated b. abortus to a titre of 1 in 500. His father kept a model dairy where nothing but Grade A milk was sold ; the cattle were all prize cattle.

His nurse had a sister suffering from the same condition in Scotland and she was a contact of the child.

CASE 4. Male, aged eight years, came from Guildford. He was taken ill in October 1934 after catching cold. His temperature ranged from 99° to 100° F. and he lost 7 lb. in weight. Some teeth were extracted, as they were thought to be the cause of the trouble. Physical examination showed nothing abnormal. The Mantoux test was negative. A blood count showed : 5,000,000 R.B.C. ; 4,700 W.B.C. with 48 per cent. of polymorphs. The undulant fever skin test was strongly positive. The agglutinations against b. abortus and b. melitensis were negative to a titre of 1 in 500. Later the test was positive to a titre of 1 in 1,500 at another laboratory.

CASE 5. Female, aged eight years nine months, was seen at Great Ormond Street on November 1, 1934. She had been ill with a temperature up to 100° F. for the previous two weeks. Physical examination showed nothing abnormal. X-rays of the chest and antra were normal. The Mantoux test was negative ; the undulant fever skin test was strongly positive. A blood count showed : 6,000,000 R.B.C. ; 8,100 W.B.C. with 56 per cent. polymorphs ; haemoglobin 100 per cent. Examination of the stools and urine was negative. Her blood agglutinated b. abortus and b. melitensis up to a titre of 1 in 500. In hospital the temperature was 100° F. on admission, but by the fifth day was normal. She was discharged at the end of three weeks well.

CASE 6. Male, aged five years, was admitted to Great Ormond Street on February 5, 1937, with a history of the sudden onset of pyrexia at the beginning of January ; the fever lasted fourteen days. The temperature was normal every morning, but rose in the evenings to 102° F. The child appeared to be quite well, but towards evening was noticeably tired and flushed. Appetite was good ; the bowels acted regularly ; there was no sickness, undue sweating, or complaint of pain. On examination he was a healthy, well-covered child with no abnormal physical signs in chest. The cardiovascular system was normal. The tonsils were small ; there was no glandular enlargement. The spleen was enlarged to about two fingerbreadths below left costal margin. The temperature was normal while in hospital. The sedimentation rate (micro-method) was 9 mm. in first hour. Mantoux and Wassermann reactions were negative. Blood count : 3,720,000 R.B.C. ; Hb. 70 per cent. ; C.I. 0·9 ; 5,200 W.B.C. ; polymorphs, 48 per cent. ; lymphocytes, 46 per cent. ; monocytes, 6 per cent. Agglutination with b. abortus was positive up to a titre of 1 in 1,000 ; there was slight agglutination with b. melitensis. [This case has been recorded elsewhere (Hardwick, 1937).]

CASE 7. Male, aged eight-and-a-half years, was seen in January 1935 with a history of a continuous temperature ranging from 99° to 101° F. for the previous few weeks. Apart from this the child appeared quite well. There was a history of contact with a case of tuberculosis, but an x-ray of the chest was quite normal. There were no abnormal physical signs ; the spleen was not enlarged. The agglutination against b. abortus was positive to a titre of 1 in 5,000.

CASE 8. Male, aged five-and-a-half years, attended the hospital in July 1934 with a history of frequent colds accompanied by a high temperature during the previous eight months. There were no abnormal physical signs, the spleen was not enlarged. An X-ray of the chest showed enlarged hilar shadows, the sinuses were clear. The Mantoux tuberculin test 1 : 1,000 was negative. In November 1934 his sister was admitted to the wards suffering from undulant fever and the agglutinations of this boy against b. abortus gave a weak positive reaction.

Discussion

Undulant fever in man is a relatively benign disease ; Dalrymple Champneys (1935) gives the mortality as 3·1 per cent. in nearly three hundred cases. No fatal cases have been reported in children in this country. The disease would appear to start in children with the signs of a catarrhal infection of the upper respiratory tract. Such infections are so common at this age that it can well be understood that many cases of this disease never reach the care of a medical practitioner, let alone that of the serologist who can make the diagnosis.

Most authorities draw attention to the insidious onset of the disease. It would seem possible that in children an abrupt onset is more usual. This was so in five of our cases, and Robertson (1934) has reported a case of a child who became acutely ill within twenty-four hours of the beginning of her symptoms.

The brucella organisms are susceptible to heat and it is probable that pasteurization is usually successful in killing the organisms. Evidence in favour of this is given by Simpson (1933), who reported one hundred and forty-two cases from Dayton, Ohio. Three years after the introduction of compulsory pasteurization in the district no case had been reported (Beattie et al., 1935). Of Dalrymple Champneys' (1934) series of cases only nine came from London. In addition, there is very little risk of the bacteria being re-introduced into the milk by those who handle it after pasteurization, as may happen in tuberculous and streptococcal infections. Cases have been reported (Jewesbury, 1937) occurring in children whose milk supply has been pasteurized, but it is difficult to exclude the possibility of the consumption of milk from another source.

The small number of cases occurring in children may be accounted for by a threefold explanation. First, many cases are not recognized; secondly, pasteurization is successful in killing any organisms that are in the milk supply, thirdly, the b. abortus and b. melitensis are but mildly pathogenic.

Thanks are expressed to Dr. D. N. Nabarro for the supply of brucellin and to Dr. E. A. Cockayne and Dr. W. J. Pearson for permission to do skin tests on their patients.

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A STANDARD INTRAVENOUS GLUCOSE TOLERANCE TEST

BY

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Since the introduction of micro-methods for the estimation of the blood-sugar the oral glucose tolerance test has been the accepted means of differentiating between the various forms of glycosuria. For this purpose it has proved both convenient and reliable. As a research weapon, however, it is less satisfactory,

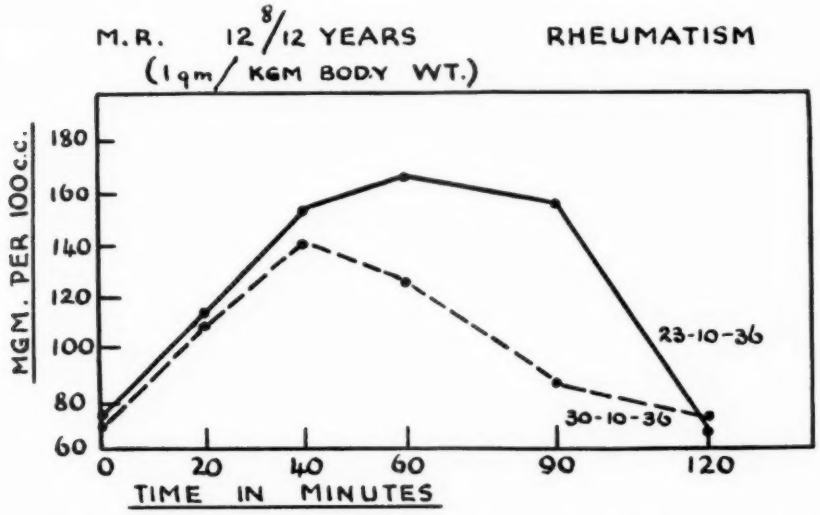

Fig. 1.—Two oral glucose tolerance tests performed at an interval of one week in a child of 12 yr. 8 mth. under standard conditions.

first because of the wide normal range and secondly because wide variations may occur from time to time in the same individual even when the tests are performed without alteration in the controllable conditions. This variability has been studied especially by Svensgaard (1931).

Adults and older children subjected to the oral glucose tolerance test on two

occasions usually give fairly similar curves ; but in a proportion of cases wide variations within normal limits are found (fig. 1). In young children such variations are more frequent, and in infants they appear to be the rule rather than the exception. In these children and infants the variations may be considerable, two curves on the same subject sometimes differing in the three important features of maximum level, time of maximum level and duration of hyperglycaemia (fig. 2). It would therefore appear that even with standardized external conditions the state of the alimentary canal itself cannot be so regulated as to produce a consistent rate of absorption.

In view of these facts, it is evident that any conclusions based on slight variations in the blood-sugar curve following oral glucose must be guarded. In

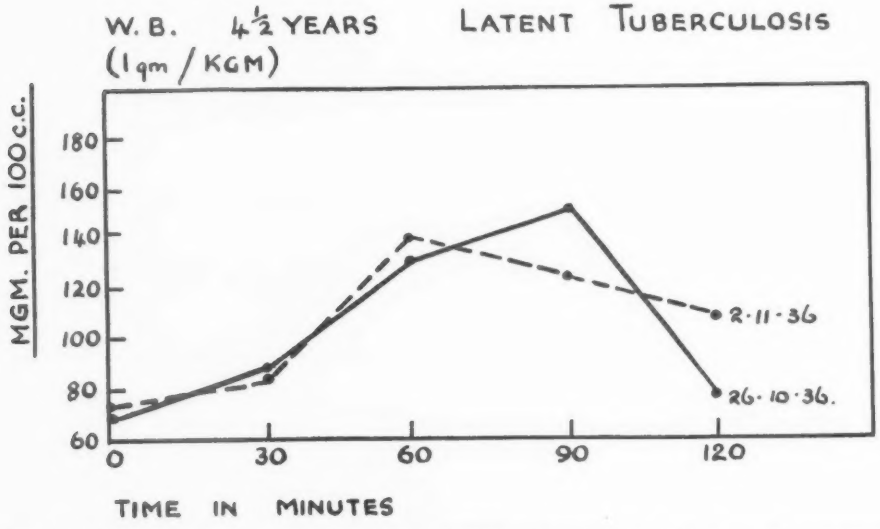

FIG. 2.—Successive oral curves showing variation in maximum level, time of maximum level and duration of hyperglycaemia.

order to exclude the variable factor of absorption, certain workers have recently studied the blood-sugar curve following intravenous injection of a glucose solution. In these circumstances absorption plays no part, so that the factors tested are the rates of utilization, storage and excretion. Unfortunately different investigators have employed widely varying dosages of glucose and modes of administration, rendering the interpretation of results, and more especially the comparison of one worker's results with those of another, matters of considerable difficulty.

The present paper is a preliminary report of a more extensive investigation of intermediary carbohydrate metabolism with special reference to children ; it presents an attempt to devise a standard intravenous glucose tolerance test applicable at all ages, and to determine the normal range and constancy of the curves obtained and what constitutes a significant variation in any particular case.

Technique of the test

Various doses and methods of administration have been employed, but the following technique has been found most generally satisfactory :

The patient has no food for eight hours prior to the test, but may be allowed water to drink. If a series of curves is to be performed on the same subject the test should be made at the same time of day on each occasion. A fasting specimen of capillary blood is removed from the lobe of the ear, or from the heel in the case of infants, and then the injection is given. The dose of glucose used is half a gramme per kgm. of body weight, and it is injected intravenously as a 20 per cent. solution in 0·9 per cent. sodium chloride. The injection is made into a vein using a 20 c.c. syringe fitted with a two-way stop-cock and

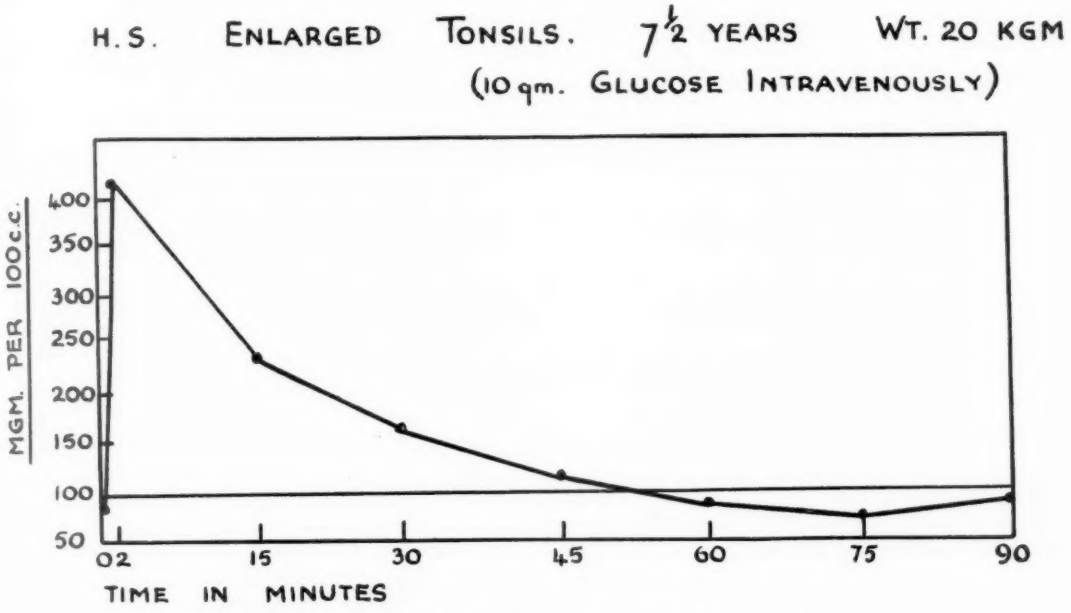

FIG. 3.—Example of typical intravenous curve in a normal subject.

rubber tubing leading to the glucose reservoir. The rate of injection can be accurately measured and the time allowed is 45 seconds for each 20 c.c. Specimens of capillary blood are removed for sugar estimation 2 minutes after the end of the injection and again at 15, 30, 45, 60, 75 and 90 minutes. The bladder should be emptied before the injection is given and again when the last specimen of blood has been taken. Blood-sugar has been estimated by a modification of the method of Hagedorn and Jensen (1923) and urinary sugar by Benedict's method (1911).

Characteristics of the normal curve

The features of a typical curve in a normal subject are illustrated in fig. 3. The blood-sugar level attains its maximum at the end of the injection and immediately begins to fall rapidly. Even when frequent samples of blood have been examined during the first thirty minutes (fig. 4) no interruption of the

steep descent of the curve in this period has been found. Ross (1936*a*), on the other hand, reports several double-peaked curves with minor rises during this phase, but does not advance any explanation of this rather unexpected finding. Fasting levels are regained in from forty-five to seventy-five minutes, and later specimens frequently show subnormal values (below 75 mgm. per 100 c.c.).

Constancy of the curve in the individual.—The concentration of the blood-sugar in the two-minute sample is of little importance. At this stage the blood-sugar is falling rapidly, so that slight variations in rate of injection, time of

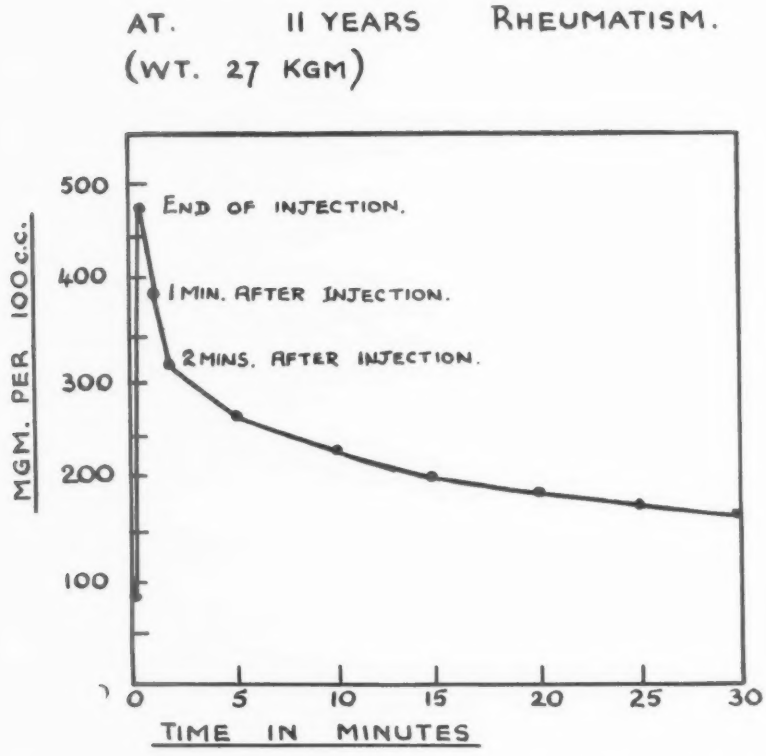

FIG. 4.—Intravenous blood-sugar curve with frequent readings during half-hour after injection of 13½ gm. glucose.

collection of the sample, and rate of flow of blood from the skin puncture may produce wide variations in this reading. In ten subjects the test has been performed on two occasions at an interval of one week. The results are given in table 1. In this table column (*a*) represents the findings on the first occasion and column (*b*) those on the second occasion. Column (*c*) gives the difference between corresponding readings in the two experiments. In five of these cases the difference between the two-minute readings on the two occasions was more than 20 mgm. per 100 c.c. ; but usually by the fifteen-minute reading and always at thirty minutes the curves were within 10 mgm. per 100 c.c. of one another—a much closer proximation of the curves than is found after successive oral

TABLE I

THE RESULTS OF TWO INTRAVENOUS TESTS ON EACH OF TEN CASES

Case ..	1			2			3			4			5			6			7			8			9			10			
	a	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	*a*	*b*	*c*	Average difference
Fasting ..	86	86	0	98	82	16	92	92	0	90	88	2	91	81	10	62	61	1	90	89	1	81	77	4	87	89	2	93	95	2	3·8
2 minutes	298	282	16	390	364	26	306	340	34	335	321	14	408	460	52	428	500	72	368	394	26	296	308	12	408	400	8	390	388	2	26·2
15 „	232	228	4	251	238	13	202	216	14	238	231	7	244	255	11	274	282	8	253	245	8	206	212	6	282	277	5	219	221	2	7·8
30 „	168	163	5	199	190	9	139	148	9	200	192	8	165	169	4	202	205	3	188	182	6	175	173	2	194	202	8	139	146	7	6·1
45 „	125	122	3	154	149	5	111	119	8	166	160	6	119	126	7	158	167	9	154	150	4	122	126	4	114	123	9	95	94	1	5·6
60 „	101	102	1	115	111	4	77	81	4	127	124	3	83	90	7	109	110	1	104	106	2	95	97	2	97	99	2	86	89	3	2·9
75 „	88	79	9	98	97	1	61	76	15	92	90	2	66	79	13	78	81	3	91	88	3	92	94	2	75	90	15	92	87	5	6·8
90 „	88	83	5	84	87	3	59	72	13	74	79	5	76	69	7	66	70	4	77	71	6	81	84	3	68	83	15	81	83	2	6·3

a = First test. Blood-sugar levels in mgm. per 100 c.c.

b = Second test. „ „ „ „ „ „

c = Difference between corresponding readings in mgm. per 100 c.c.

glucose tests. Occasionally subnormal blood-sugar values were found seventy-five and ninety minutes after the injection. When this occurred there was sometimes a relatively wide separation between the two readings at these times (table 1, cases 3 and 9).

The normal range : variation with age.—A considerable degree of constancy of the curve at different times in the same individual has thus been demonstrated, and it remains to consider the amount of variation between normal subjects. For this purpose fifty-three normal or convalescent individuals in whom no abnormality of carbohydrate metabolism was suspected were submitted to the test. On comparison of the results obtained the most constant feature was found to be the time at which normal fasting levels were regained. The upper limit of the fasting level in the present normal series was found to be 100 mgm. per 100 c.c. and the times at which the first readings at or below this level were obtained are summarized according to age groups in table 2. Although the number of cases in some of the age groups is small, these figures show that the power of the infant, relative to body weight, to utilize and store carbohydrate is high ; and that this so-called high carbohydrate tolerance falls off progressively during childhood until the adult level is reached in the ten to thirteen year age group.

TABLE 2

SUMMARY OF TIMES AT WHICH FIRST BLOOD-SUGAR READING AT OR BELOW 100 MGM. PER 100 C.C. WAS OBTAINED

Age groups . .	0–2	2–4	4–7	7–10	10–13	Adults.
No. of cases	4	6	18	11	8	6
Fall in 15 min.	—	—	—	—	—	—
,, 30 ,,	75 per cent.	—	—	—	—	—
,, 45 ,,	25 ,,	50 per cent.	33 per cent.	18 per cent.	—	—
,, 60 ,,	—	50 ,,	50 ,,	46 ,,	35 per cent.	50 per cent.
,, 75 ,,	—	—	17 ,,	36 ,,	63 ,,	50 ,,
,, 90 ,,	—	—	—	—	—	
Average of injected glucose excreted in urine.	4 ,,	5·1 ,,	8 ,,	5 ,,	7·8 ,,	8·5 ,,

Discussion

As indicated above, the test described has been devised for research purposes rather than for use as a diagnostic procedure. Jorgensen and Plum (1922) used an intravenous test for the differentiation of malignant and benign glycosurias, claiming that their test gave a smaller proportion of doubtful results than are obtained with an oral glucose tolerance test. They employed a con-

stant dosage of 20 gm. glucose in 50 c.c. of water, and for the assessment of the results Jorgensen (1926) introduced the ' loading figure '—the sum of the area of the curve above the fasting level in sq. cm. and the time in minutes for the fasting level to be restored. This technique was not adopted in the present experiment for the following reasons :

1. The projected work was to be conducted on children, so that variation of dosage with body weight was considered essential. An infant weighing 5 kgm. and having a blood volume in the region of 400 c.c. could hardly be subjected to the same injection as a child of twelve years of age with a blood volume between three and four litres if the resulting curves were to be comparable.

2. In comparing the effects of glucose injections using water and physiological saline as solvents it was found that not only were nausea and pyrexia more frequent after the water injections but also that the blood-sugar level behaved in a more erratic manner than when the injection was made with saline. For this reason all the injections in the present series have been made with the glucose dissolved in 0·9 per cent. sodium chloride solution. Ross (1936*a*, 1936*b*) employed water as the solvent, and it is possible that the upset of osmotic equilibrium produced accounts for the double-peaked and irregular curves which he reports ; but Jorgensen also employed a watery medium and he reports no such findings.

3. The introduction of such a mixed and artificial factor as Jorgensen's ' loading figure ' was considered undesirable, especially when it was found that the type of the curve could be accurately defined by reference to the time at which the first blood-sugar reading at or below 100 mgm. per 100 c.c. was obtained.

The choice of this point—the time of restoration of the blood-sugar to 100 mgm. per 100 c.c.—possibly requires some explanation, the usual point taken by other workers being the time at which the original fasting value has been regained. In children to a greater degree than in adults the fasting value fluctuates from time to time, and after eight hours' fasting it tends in many cases to be about the lower limit of normal (table 1, cases 5, 6 and 8). In these circumstances it seems fairer to judge the intermediary mechanism by its ability to restore a normal fasting blood-sugar level rather than the actual level present when the test commenced.

The technique of Jorgensen and Plum has been widely followed by other Scandinavian workers, including Torning (1932), Thaysen (1932) and Morgensen (1927). These latter workers employed the test in an attempt to explain the ' low blood-sugar curve ' (Thaysen, 1932) of non-tropical sprue. Ross (1936*a*) employed an intravenous test, using 10 gm. glucose in 50 c.c. of water in an investigation of carbohydrate absorption in coeliac disease and abdominal tuberculosis ; and an intravenous glucose tolerance test was also used by Fikri and Ghalioungui (1937) to elucidate abnormal oral glucose curves found by them in ankylostomiasis. They employed a dosage of $\frac{1}{3}$ gramme glucose per kgm. of body weight, but they do not state in what concentration the glucose was injected.

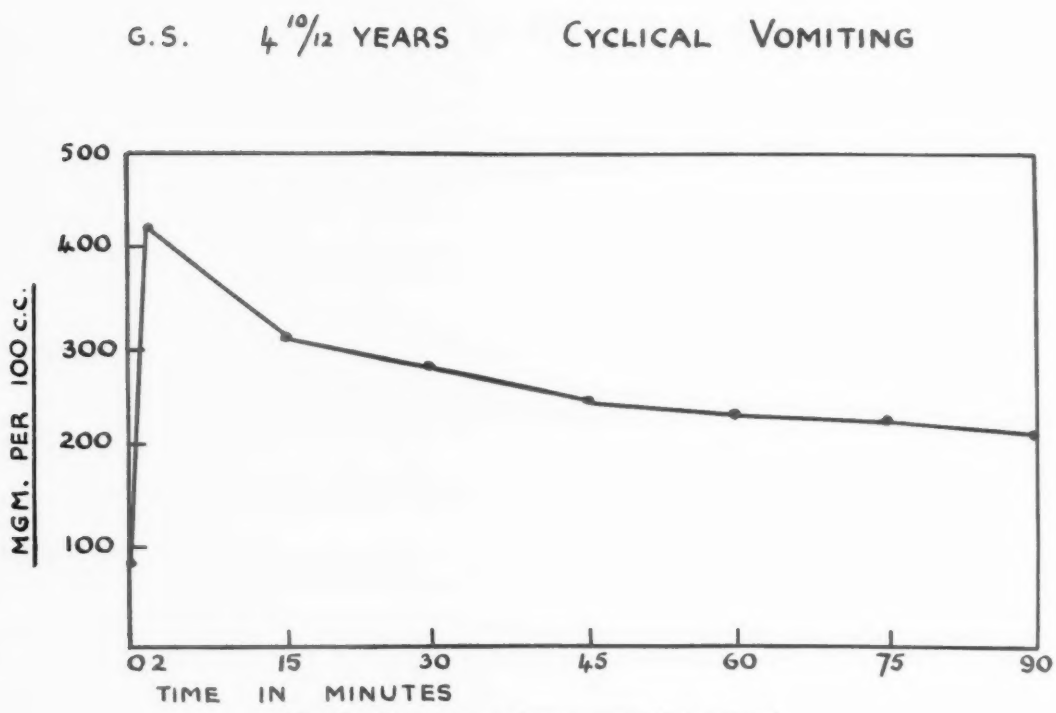

FIG. 5.—Intravenous glucose curve during attack.

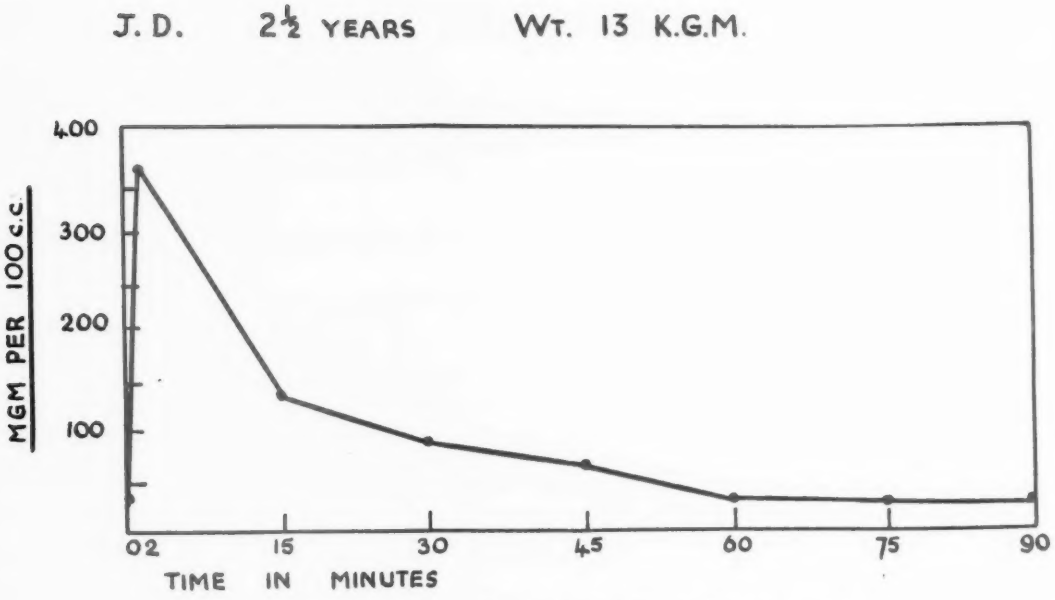

FIG. 6.—Intravenous glucose curve twelve hours after a convulsion.

Conclusions

The test which has been described presents clearly defined normal limits : it can be stated that if the fall to 100 mgm. per 100 c.c. occurs in less than forty-five minutes in children between two and ten years of age, or in less than sixty minutes in children over ten years of age, then increased tolerance is present. If, on the other hand, the fall to 100 mgm. per 100 c.c. is delayed beyond sixty minutes in children under four years of age, or beyond seventy-five minutes above that age then there is some degree of impairment of the carbohydrate tolerance. These statements for the lower age groups are made with some reservation owing to the small numbers of the younger children examined.

The constancy of the curve in the individual (table 1) is such that a change in the time at which the first reading of 100 mgm. per 100 c.c. or less is obtained may be accepted as evidence that a change of tolerance has occurred—a diminution in tolerance if the time has increased and a rise of tolerance if the time has diminished.

From this work it would seem that the intravenous glucose tolerance test gives a more reliable estimate of the intermediary carbohydrate metabolism than does the oral test. The question whether significant variations occur in pathological conditions is at present under investigation. Examples of abnormally slow and abnormally rapid fall are illustrated in figs. 5 and 6 respectively. The former is from a case of cyclical vomiting, the latter obtained during the upset of carbohydrate metabolism which frequently follows a convulsion (McLean, 1936).

Summary

An intravenous glucose tolerance test is described, applicable to children at all ages, as well as to adults. The dosage employed is half a gramme of glucose per kgm. body weight, injected as a 20 per cent. solution in 0·9 per cent. sodium chloride. Carbohydrate tolerance is gauged by the time taken for a normal fasting level to be attained. The test shows a high degree of constancy for the individual ; and the limits of normality are well defined. The blood-sugar curve descends more rapidly in young children than in adults.

Thanks are due to Professor G. B. Fleming and Dr. Noah Morris for valuable criticism and advice. This work was carried out during the tenure of a Hall Tutorial Fellowship.

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CASE REPORTS

PARAPLEGIA AND MONGOLISM IN TWINS

BY

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Clinical record

M. G., aged four years and six months, was an undoubted mongol, showing the typical signs of round head, slanting eyes, broad face and incurved little finger. She had an internal strabismus and chronically inflamed conjunctivae. She suffered from a paraplegia, a condition rarely seen amongst mongols. On examination of her nervous system the following data were obtained : There was marked spasticity of the legs, especially of the ankles. She walked unsteadily in the equino-varus position, the heels only occasionally reaching the ground. On attempting to rise off the floor she showed a marked ' cuisse-tronc ' sign and then could only raise herself by getting on to all fours. Her arms were normal as to muscular tone, reflexes and voluntary movements, but showed a slight degree of choreic movement. Her legs were hypertonic, paretic, showed exaggerated tendon reflexes, the knee-jerks being obtained from well down the shins (i.e. Strumpell's sign was positive). The plantar reflexes were extensor, but the Oppenheim reflexes were negative. No clonus was obtained. There was no evidence of cerebellar dysfunction.

Physical examination of the twin sister

On enquiry it was found that she had a twin sister (G. G.) who was declared by the mother to be normal. This child was brought by her mother for examination, and although she might not be remarked as a mongol when seen casually, several experienced observers agreed that she should be diagnosed as such, although the characteristics were certainly less pronounced than in the case of her sister. A careful examination of her nervous system showed only a slight degree of choreic movement in her arms, a slight degree of the ' cuisse-tronc ' phenomenon on rising to a sitting from a recumbent position and a doubtfully extensor plantar response on the right side. Otherwise there was no appreciable disability in her various systems. The slight positive ' cuisse-tronc ' sign and doubtful plantar reflex on one side are insufficient to warrant a diagnosis of a clinical syndrome of pyramidal defect or damage in a child of this age, though such disturbance cannot be wholly excluded.

The nature of the twinning

The question as to whether the twins were identical or not was obviously of the first importance. The hair and eye colour were strikingly similar, but in other respects there was no difficulty in distinguishing between the two. However, as the chief differences could be attributed to the presence of paraplegia and a greater degree of mongolism in M. G. and as they did not seem to exceed those sometimes found in accepted identical twins, the diagnosis could only be made by means of further tests :

1. The blood groups were kindly determined by Dr. H. C. Heathcote, who found that both twins were A. and both were M.

2. Next a series of skiagraphs were taken by Dr. G. D. Steven of the limbs. The lower limbs showed no appreciable difference in the stage of ossification, but in the upper limbs there were distinct differences. In M. G. the centres for the heads of the radii had appeared, but not in G. G. ; further, while M. G. had well developed centres for the medial epicondyles, G. G. had an extremely small one on one side only. It is interesting to note that so far as there were differences the more obvious mongol was more advanced in this respect than her twin sister. This finding made it unlikely that the twins were identical, for it is known that differences in rate of ossification of any appreciable degree are not found in identical twins (Bushke, 1935).

3. Finger-print investigation. The finger-prints of both children were submitted to Dr. Percy Stocks, whose extensive work (1930 and 1933) on this question has shown that the determination of the type of twinning can be made with considerable confidence. Dr. Stocks reported fully, and we are greatly indebted to him for his assistance. One thumb print was not clear enough for examination, but a comparison of the other nine prints showed only one pair similar (defining similar as in the paper by Dr. Stocks). Dr. Stocks states that with one exception only, he has never seen twins with less than four similar pairs of prints, whose physical characteristics suggested identity. These exceptional twins had only one similar pair, but he has suggested that the case was one of those instances in which close physical resemblance occurs in fraternal twins, as indeed it may do occasionally in brothers or sisters born at different times.

The evidence from finger-prints alone, therefore, makes it almost certain that M. G. and G. G. are fraternal and not identical twins, and this confirms the evidence afforded by the different stages of ossification at the elbow and the general lack of close physical similarity.

Mental examination of the twins

M. G. (paraplegic) : Chronological age four years six months ; Mental age two years eight months ; I.Q. 59.

This result was made up as follows : She passed all the two-year tests standardized by Gesell. She passed three only of the Binet three-year tests. She could name objects shown to her, name objects in pictures and give her last name, but failed the other three-year tests. She could count four pennies, but failed all the other four-year tests. She passed nothing above the fourth year.

G. G. : Chronological age four years six months ; mental age four years ; I.Q. 89.

These tests were made on the ordinary Binet scale.

WHOLE FAMILY. Mother. D.G. M.G. M. G. G. G.

The remainder of the family.

FATHER, aged 38, was healthy. His occupation was a builder's labourer. His family history was reported negative.

MOTHER, aged 31, was healthy. Her family history was reported negative.

HALF-BROTHER, D. G., son of the mother, aged eight years nine months, was healthy. His mental age was nine years one month ; I.Q. 104.

BROTHER, M. G., aged five years nine months, was healthy. His mental age was six years six months ; I.Q. 113.

Many normal persons show traits which might be considered at least mongoloid, but it was notable that in general appearance the parents and the two brothers were not in any way of this type, which increased our confidence in diagnosing G. G. as a mongol.

Discussion

Paraplegia in mongols.—It would appear from the literature that paralysis is very rare amongst mongols.

Brousseau (1928) states that she has seen two cases of mongols with paralysis, one being a girl of four years seven months with congenital spastic paralysis ; no details are given with regard to the other. Stevens (1915) in an article on the relationship of syphilis and mongolism describes two cases of spastic paralysis out of a series of twenty, one in a girl of two years six months and the other in a boy of seven years. Tredgold (1929) in his description of mongolism makes no mention of the occurrence of paralysis.

There is, therefore, no reason to suppose that the paraplegia in this case has any relationship with the mongolism as such.

No certain knowledge exists as to the precise cause of either infantile paraplegia or of mongolism. Paraplegia is generally supposed to be of

(1) Spinal origin due to birth injuries of the spinal cord, but in these cases there is no reason to expect mental deficiency unless it is coincidental, and almost all such cases occur in breach presentations. In this case there was no history of abnormal labour.

(2) Cortical origin due to injury to both leg areas presumably at least in some cases consequent upon lesions of the longitudinal sinus at or about the vertex.

(3) It is generally agreed that at least a proportion of cases of diplegia (Little's disease) is congenital in origin, i.e. due to failure of development, and so it is possible that some cases of paraplegia with no appreciable involvement of the arms may be due to the same cause.

So far as mongolism is concerned many theories have been advanced, most of which have proved untenable on more extensive examination. Penrose (1932) concludes that the condition has a hereditary basis, but that whether a potential mongol becomes a mongol in fact, depends on non-genetic post-fertilization factors the nature of which is unknown, except that advanced maternal age is sometimes a factor.

Mongolism in twins.—The familial incidence of mongolism is small. Penrose

(1933) states that about one mongol in fifty has a similarly affected brother or sister. It would be expected, therefore, that in the case of fraternal twins one of which was a mongol, the other would nearly always be normal. In the case of identical twins, however, both would be affected.

Penrose (1932) states '. . . the curious fact that although cases of like-sexed twins, both affected, have been observed, there is no instance on record of twins both affected and of different sexes. The explanation seems to be that while in the case of identical twins neither is more likely to miscarry than the other, in the case of twins which are both affected but binovular, one twin nearly always miscarries.'

It should be explained that Penrose brings forward evidence to show that the mothers of mongols show a relatively high rate of miscarriage and that deaths of their children in infancy, before a diagnosis of mongolism could be established, are also disproportionately numerous. The deduction is that the number of mongols eliminated by pre-natal and early post-natal deaths may be greater than the number of mongols observed, perhaps considerably greater. As regards twins, Penrose quotes two of his own cases in each of which a mongol was born following the previous miscarriage of a twin foetus. While, therefore, fraternal twins both of whom are mongols would in any case be rare owing to the low familial incidence of the condition, the additional complication of early death so reduces the proportion that no proved case appears to be on record. The present case, therefore, is of interest as being an example of fraternal twins both of whom are mongols and both of whom have survived the period of infancy.

Variation of degree of mongolism.—No authority has yet succeeded in laying down absolute criteria for the diagnosis of mongolism.

Tredgold (1929) remarks '. . . these anomalies are not distinctive in themselves. As a matter of fact, many ordinary aments, and even normal individuals, possess one or more of the peculiarities which go to the make up of mongolism. It is the combination which is so characteristic of this condition. But where this combination occurs it produces a picture which is so distinctive as to constitute a definite and readily reconizable clinical variety.'

It must therefore be a matter to some extent of personal judgement as to whether any particular individual should be diagnosed as a mongol or not, but for reasons given above we are satisfied that the second twin G. G. should be so regarded. If this diagnosis is accepted not only is the occurrence of mongolism in a pair of fraternal twins of interest, but also the relatively high mental age of G. G.

This is in accordance with the observation of Tredgold (1929) who states that ' the degree of mental defect varies very considerably and on the whole I am inclined to think that there is a direct relation between this and the intensity of the physical signs.'

Most studies of mongols in the literature have been undertaken on mental defectives and nearly always those in institutions. Even so Tredgold notes

that some mongols may be merely feeble-minded. Even allowing for more than usual retardation in mental growth an I.Q. of 89 at four years six months makes it improbable that G. G. will fall into the category even of the feeble-minded, as this raises the question as to how far some degree of mongolism may not occur in persons usually regarded as normal. It is striking that if an observer sets out to look for the presence of mongolian characteristics in the members of communities other than those in institutions for mental defectives, it is possible to select a certain number of individuals who might well be included within the diagnostic bounds of mongolism. We are not aware that any observations on these lines have been systematically made ; nor is this surprising since all observers probably tacitly assume that mental deficiency is an essential criterion of mongolism. Further, if the contention of Tredgold is accepted that the physical features become less marked as intelligence rises, mongols of normal mentality, if they exist, would not be likely to possess such marked features as to excite the attention of the ordinary clinical observer unless he were specially on the look-out for such cases. None the less, observations of such cases, if they can be found, might provide information of great importance for the elucidation of the causation and nature of this very obscure condition.

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A FOREIGN BODY IN THE KIDNEY

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Urinary infection is frequently due to or accompanied by the deposit of calculi, and in these circumstances it is notoriously difficult to treat the infection satisfactorily so long as the foreign body remains. Rarely a foreign body introduced into the bladder per urethram is found to be the cause of chronic pyuria. Still more rarely—as in the case here recorded—a foreign body may ulcerate through the wall of some part of the alimentary tract into the kidney, ureter or bladder and give rise to urinary infection.

Case record

A female child aged four years, of healthy parents and with good personal history, developed symptoms of cystitis (increased frequency of micturition, with specks of blood in urine) in June 1935. She received home treatment and apparently responded fairly well, but the urine never became free of pus cells, and when first seen (by N. B. C.) in January 1936, she had developed a recrudescence of haematuria following an attack of tonsillitis three weeks previously. Micturition was neither frequent nor painful, but there was some impairment of general health with loss of appetite, slight wasting and lethargy. A history that the child had swallowed a small metal hair-slide early in 1935 was given, but little importance was attached to this statement.

Examination of the patient showed her to be a pale and debilitated child weighing 35 lb., with coated tongue and unhealthy tonsils. The lower pole of the right kidney was distinctly palpable but not tender ; the genitalia were slightly inflamed ; the urine was white in colour, turbid, alkaline in reaction and contained numerous pus cells, with a few erythrocytes. There was no oedema, no rise of blood-pressure (systolic pressure 75 mm. Hg), no abnormality of the optic fundi, no organic lesion in the heart, no enlargement of the lymphatic glands and no obvious congenital malformation.

It was decided to give a course of medical treatment, and to submit the patient to further investigation if she did not respond satisfactorily within two or three

weeks. Acid therapy accompanied by hexamine and then by mandelic acid was unsuccessful, and the patient's general health deteriorated. Furthermore,

FIG. 1.

her temperature became very variable, rising to 101° or 102° F. each evening, and a tender swelling of the right kidney was easily palpable. It was obvious that special investigation was essential, and the following results were obtained.

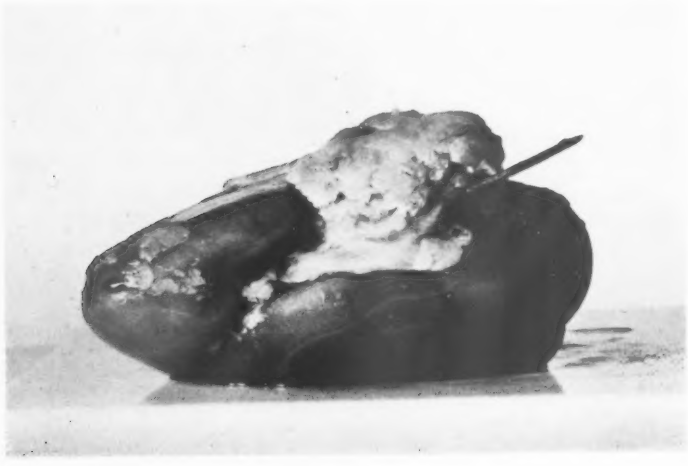

FIG. 2.

The urine contained much pus and many colon bacilli. A 'straight-through' x-ray showed an enlarged right kidney. It also showed the hair-

slide, of a variety known as the ' Kirbigrip,' apparently in the second part of the duodenum (fig. 1). This is the common position for such bodies to come to rest, as they find difficulty in negotiating the double bend of the duodenum below this level. An intravenous urogram showed a normal kidney on the left with a normal bladder, but no function on the right. No further investigation seemed desirable. A diagnosis of right-sided pyonephrosis was made, and operation was decided upon. It was thought that nephrectomy would probably be necessary.

Under general anaesthesia, the right kidney was exposed and explored. It was enlarged, engorged and oedematous. In sweeping the index finger over the anterior surface of the pelvis of the kidney, a rigid structure was felt and recognized as the Kirbigrip in the duodenum. Further exposure demonstrated an astonishing state of affairs. The hair slide had perforated the posterior duodenal wall and entered the pelvis of the kidney. The greater part of its length actually lay within the kidney substance, about half an inch remaining in the duodenum, which was, as it were, pinned to the anterior surface of the kidney. As the nephrectomy was completed, the pin was withdrawn from the duodenum, in which the small puncture was careful repaired. The wound was closed except for the usual drainage tube.

Convalescence was uneventful, the much-dreaded complication of duodenal fistula happily not arising. The greatest possible satisfaction was manifested by the child's grandmother, who had always maintained that all the trouble dated from the swallowing of the hair-slide ! The photograph (fig. 2) shows the kidney exactly as removed, with the hair-slide transfixing its substance.

Thanks are due to Dr. David Johnston (Birkenhead) for kindly referring this patient to us, and to Dr. J. H. Mather for the skiagraph.

INTRACRANIAL HAEMORRHAGE IN THE NEW-BORN

A study of diagnosis and differential diagnosis based upon pathological and clinical findings in 126 cases

BY

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Hitherto interest in intracranial haemorrhage in the new-born has been centred mainly upon etiology and pathology. More recently symptomotology has received increasing attention. While the pathology of the subject in its relation to etiological factors has received considerable attention, few attempts have been made to correlate pathological with clinical findings. The present paper is based upon both clinical and pathological observations made by the writer in connexion with 126 new-born infants in whom intracranial haemorrhage was found at autopsy. Of the 126 infants, 110 were born in the Royal Maternity Hospital and ten in the Western General Hospital, Edinburgh. Six infants were born at home, four being subsequently admitted to the Royal Maternity Hospital and two to the Western General Hospital. Infants born in hospital were under observation from the time of birth and were examined daily following the first evidence of failure to progress or of disturbed health. Clinical findings were recorded at the time of examination. A similar routine was adopted in the case of infants born at home and subsequently admitted to hospital. Post-mortem examinations were carried out within thirty-six, forty-eight and seventy-two hours of death in the case of ninety-five, twenty-four and seven infants respectively.

A pathological basis has been considered as best suited to the study of the present series. Intracranial haemorrhage found post mortem in the 126 cases included in the investigation differed according as it had taken place into the subdural space, the subarachnoid space, the ventricular system or into the brain substance. Cases have been grouped according to the distribution of the

intracranial bleeding, and clinical observations and pathological findings are discussed in relation to each group.

Subdural haemorrhage

Subdural haemorrhage was found at sixty-two autopsies. Nineteen infants were premature, thirty-four were born at term and nine were post-mature. First pregnancies numbered forty-four. There were twenty-five spontaneous deliveries, including eight breech presentations. Forceps were applied in thirty-six cases, in sixteen of which application followed manual or instrumental rotation of the head, and in two of which application was to the after-coming head in breech deliveries. There was a history of eclampsia in two and of pre-eclamptic symptoms in four mothers. The late stages of two pregnancies were characterized by hyperemesis and of one by slight ante-partum haemorrhage. Two mothers, of whom one was known to be suffering from gonococcal infection, received ante-natal treatment for leucorrhoea.

Pathological findings.—Bleeding arose from different types of injury. Rupture of the superior longitudinal sinus was associated with gross overlapping of the occipital by parietal bones in one case ; tearing of veins opening into this sinus was the cause of haemorrhage in three cases in which over-riding of the parietal bones was a feature. Haemorrhage was a sequel to sinus thrombosis (aseptic) in four premature infants. The superior longitudinal sinus was involved in one and the straight sinus in three cases. Bleeding arose from vessels involved in tentorial tears in forty-two cases (fig. 1) ; tears of the falx cerebri were rare, did not occur alone and did not give rise to haemorrhage. The source of the bleeding was not discovered in two infants. In ten cases the only finding was extensive haemorrhage between the dural layers of the tentorium or falx cerebri or both (fig. 2).

There was variation in the extent and distribution of the haemorrhage. The blood at autopsy was semi-fluid or clotted. Bleeding from the superior longitudinal sinus (and tributaries) and the straight sinus did not extend below the level of the tentorium ; infratentorial haemorrhage arose in every instance from tentorial tears usually involving the free crescentic margin. Haemorrhage from tears situated more laterally in the tentorium collected in the cranial fossae and, sometimes, spread upwards over the cerebral hemispheres, and gravitated below the tentorium only when massive. Pressure by masses of blood clot upon the medulla was a common finding in cases of infratentorial haemorrhage ; in several cases similar pressure on the fourth ventricle had resulted in considerable ventricular dilatation.

The findings in three cases of tentorial tears pointed to there having been a recurrence of haemorrhage ; the cranial fossae contained a large amount of red fluid blood, removal of which exposed old blood clot, brown in colour and adherent to the dural surfaces (fig. 3).

There was evidence of arrested haemorrhage and partial absorption in five infants. Death in these cases occurred during the second and third week of life and was due to gastroenteritis (three), septicaemia following dermatitis (one)

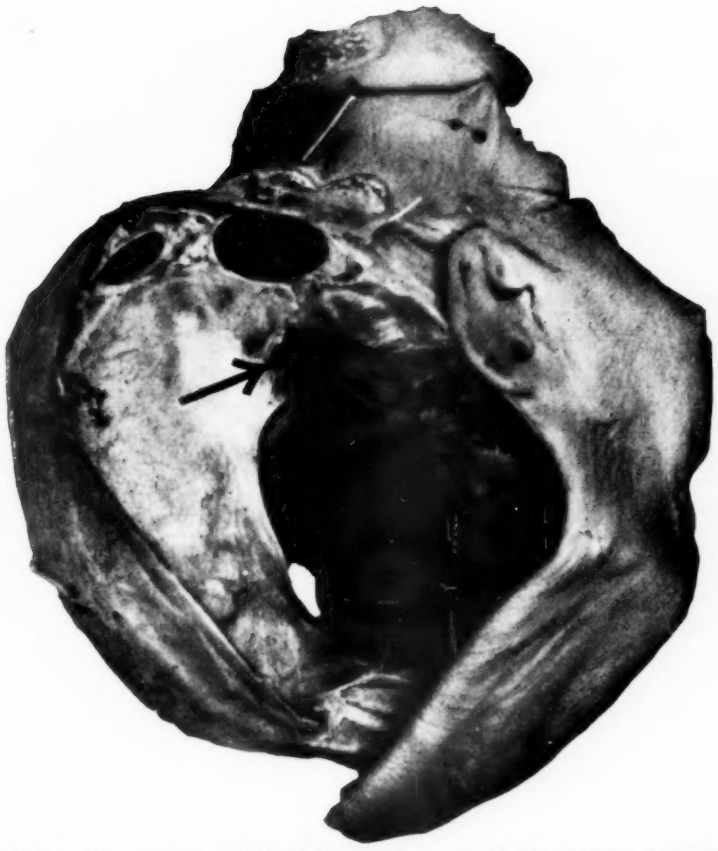

FIG. 1.—Case No. 43. Case of subdural haemorrhage in which bleeding had originated from the tentorial tear marked with arrow and gravitated below the level of the tentorium. The upper surface of the subtentorial clot is seen projecting above the margins of the tear.

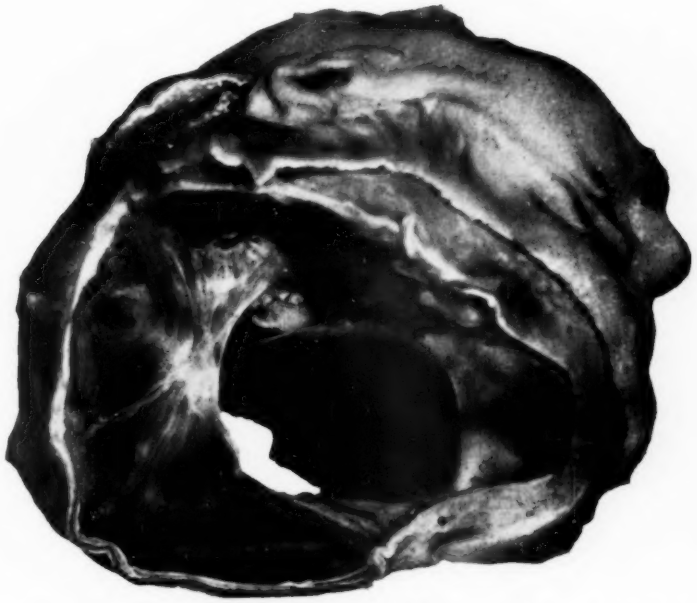

FIG. 2.—Case No. 74. Case of subdural haemorrhage. Haemorrhage is mainly supratentorial and the clot lying on the tentorium conceals the tentorial tear from which bleeding originated. The dense portions of the falx cerebri correspond to an extensive haemorrhage enclosed by the two dural layers.

FIG. 3.—Case No. 198. A case of subdural haemorrhage arising from tentorial tears in which apparent clinical recovery from severe symptoms was followed by a recurrence of massive haemorrhage, which was associated with a return of symptoms on the thirteenth day and followed by death on the fourteenth day. At autopsy the brain surfaces were covered and the cranial fossae filled by fluid and partially clotted blood which when removed revealed old, changed blood clot which was adherent to the dural surfaces as shown in the figure.

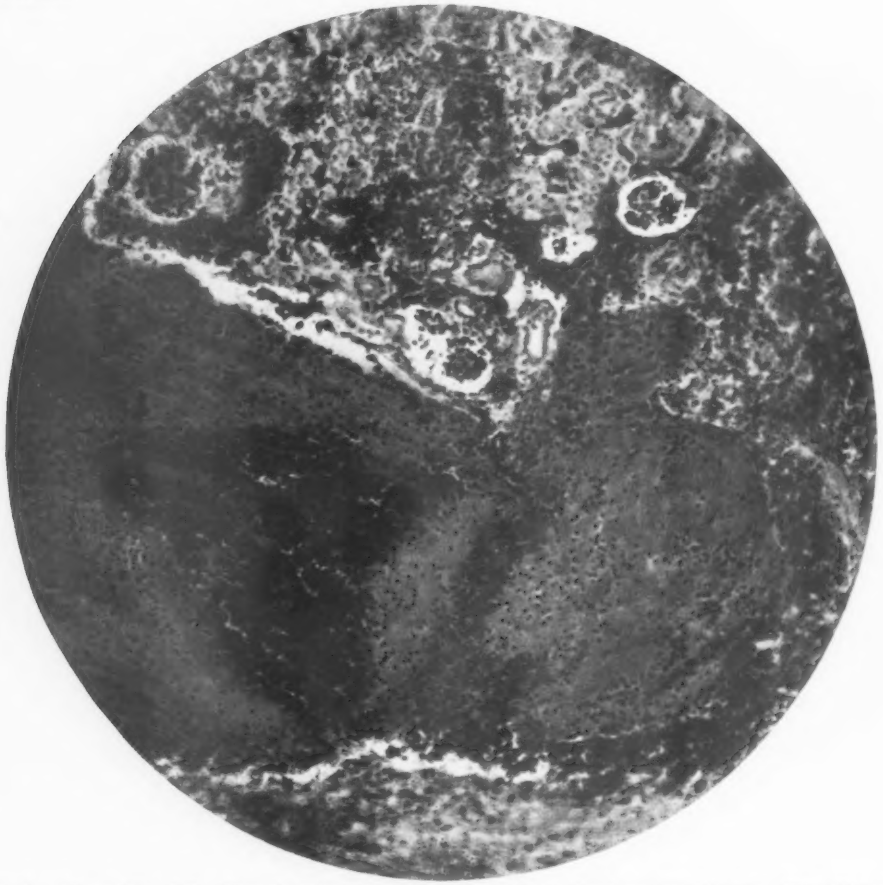

FIG. 4.—Case No. 86. Renal infarction in a case of cerebral haemorrhage. Bleeding has extended into the interstitial tissues and red blood cells are present in the tubules. Leucocytic infiltration is limited.

and pyelonephritis (one) ; in one case it followed an operation for volvulus. In each instance haemorrhage had arisen from a tentorial tear : old altered blood still remained attached to the dura lining the cranial fossae ; neighbouring structures were slightly pigmented and in three cases blood clot was attached to the lacerated tissues. Microscopically, there was active phagocytosis of degenerate red blood corpuscles.

Pathological evidence of asphyxia was a frequent finding in the form of right-sided cardiac dilatation and petechiae in relation to the heart, great vessels and thymus ; it was a constant finding in cases living only a few hours, and was seen in a large proportion of those with infratentorial haemorrhage. Some degree of atelectasis was present at all autopsies, and pneumonia and/or intrapulmonary haemorrhage in twenty-three cases ; renal infarction (fig. 4) and suprarenal haemorrhage were each found in five cases. During the period of the investigation dural tears of limited extent, not associated with bleeding, were found at fourteen autopsies not included in this series.

Clinical observations

(A) INFANTS DYING WITHIN THIRTY-SIX HOURS OF BIRTH.—Ten infants are included in this group. All were severely shocked at birth and a condition of complete collapse persisted until death. Colour remained pale but was subject to transient, deep, cyanotic changes, ; respirations were rapid, shallow and often irregular ; occasionally breathing was gasping in character and sometimes noisy as a result of mucus collected in the trachea. The pulse was imperceptible and the temperature subnormal. Tendon and conjunctival reflexes were absent or only elicited with difficulty ; there was no response (normal or abnormal) to external stimuli and no evidence of motor irritation ; the fontanelle was neither depressed nor bulging. A cry was heard in three infants ; it was weak and whimpering. Death occurred after a phase indistinguishable from coma. The intracranial bleeding was massive in all ten cases and in eight had collected in large subtentorial clots around the brain stem. Pulmonary lesions (haemorrhage or pneumonia) were present at six of the autopsies.

(B) INFANTS SURVIVING MORE THAN THIRTY-SIX HOURS.—Fifty-two cases fell into this category. They include the ten infants in whom intracranial findings at autopsy were limited to haemorrhage between the layers of the tentorium or of the falx cerebri. Death in these cases resulted from conditions related to other parts of the body ; the intracranial condition gave rise to no symptoms or signs, and these ten cases have not been included in the discussion that follows.

Of the remaining forty-two infants thirty-five were distressed at birth : in some there was definite asphyxia, in others considerable exhaustion, but in no case was there extreme shock. There was no appreciable improvement in the general condition of two infants. In the case of forty infants there was gradual and eventually complete recovery from the state of post-natal depression except in so far as there was no apparent inclination for fluids. Vomiting was a common early feature : it usually occurred on the first or second day of

life, rarely later, and in any one case only on a few occasions and at long intervals. It was not related to feeds or to the swallowing of mucus, and was moderately forcible. The vomitus was blood-stained in several instances. The facial expression became increasingly one of mental restlessness and distress, and contrasted with the existing physical inactivity. This early characteristic change was appreciable on the first day of life in three cases, on the second day in sixteen, and on the third, fourth and fifth days in five, four and one respectively ; it occurred as the first evidence of trouble in the second week of life in the two remaining cases. These infants lay awake with widely opened eyes for prolonged periods : their eyes followed moving objects or were directed towards the sources of sudden or loud sounds. The apparent interest of these infants in their surroundings was unnatural ; their expression conveyed an impression of apprehension and was that of children several months old rather than of new-born infants. These were very constant findings, as were those relating more particularly to the eyes. Blinking was common. The majority of cases showed darting, lateral movements of the eyes which were frequently stimulated or aggravated by sudden fright (e.g. due to noise). True nystagmus subsequently developed in a proportion of these cases. Other occasional findings included ptosis and strabismus. Ptosis was present at birth and tended to lessen in prominence ; strabismus developed sometime after delivery and became more pronounced. Inequality of the pupils was common. Small conjunctival haemorrhages occasionally appeared on the second or third day, but these were not confined to infants suffering from intracranial conditions.

Convulsive movements were seen in half the children included in this group and were usually preceded by a cry ; they occurred as terminal events in five cases. Eleven infants had generalized convulsions ; in six there was only slight twitching of the extremities or face. Physical examination, feeding and sudden noises all on occasion provoked fits. In only three cases was a relation established between the localization of the twitching and the distribution of the haemorrhage. Other abnormalities were athetoid movements of the arms in four and a persistent fine tremor of the hands in two infants.

Crying was not a constant finding. It was present in 50 per cent. of cases ; was shrill or piercing ; occurred in infants in whom abnormal fullness of the fontanelle had been previously detected ; and frequently heralded the onset of convulsions. ' Sponginess ' of the fontanelle was more common than great tension. Extensive haemorrhage over the vertex was a feature of three of the five cases in which bulging of the fontanelle was appreciable during life. Retraction of the head and nuchal rigidity were rare and limited to cases with infratentorial haemorrhage.

The condition of the tendon reflexes varied in different subjects and in the same subject. Usually they were diminished in the early stages, exaggerated during the period of mental restlessness and absent during the terminal phase. Increased muscular tone developed in a large number of cases and persisted throughout life. It was most marked in the upper limbs and to a lesser extent in the legs ; in severe cases the fingers were firmly flexed over the thumbs and the arms were kept in a state of spastic flexion over the chest. Although tested

for as a routine, facial irritability was detected on only three occasions ; twitching of the upper lip upon tapping the tip of the nose (Catel's sign) was obtained more frequently, but was of doubtful significance. An observation of greater diagnostic value was the repeated, quick, darting protrusion of the tongue seen in a number of these infants. The rapid movements have given rise to the term ' adder tongue ' : they are readily distinguished from the more sluggish and less precise movements of the tongue in thirsty or dehydrated infants.

Pallor was a common and cyanosis a constant finding. Cyanosis appeared at different stages in the clinical course of the condition ; it was subject to spasmodic aggravation and was occasionally diminished by the administration of oxygen. It was most pronounced in infratentorial haemorrhage (fig. 5).

The character of the pulse varied, although always rapid and soft in the

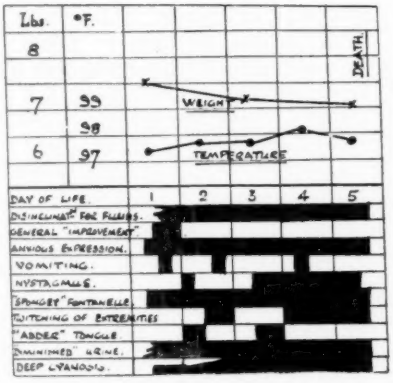

FIG. 5.—Case No. 47. Subdural haemorrhage below the tentorium in a first child delivered by forceps after previous instrumental rotation of the head. Symptoms of cerebral haemorrhage were present on the day of birth and persisted throughout life. At autopsy a large tentorial tear and extensive pneumonia were found.

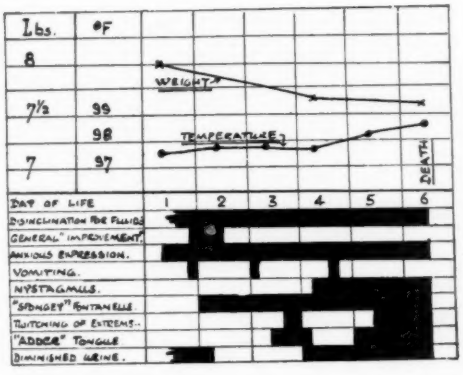

FIG. 6.—Case No. 161. Subdural haemorrhage above the tentorium in a first child delivered by forceps after previous manual rotation of the head. The presence of intracranial haemorrhage was suggested on the day of birth by the facies and confirmed by the appearance, during the next forty-eight hours, of confirmatory signs which persisted throughout life. An extensive tentorial tear was found at autopsy.

terminal phases ; its most constant characteristic was a deliberation resulting from slowness and fullness. In the early stages respirations were slow and shallow, later they deepened, but again became shallow with an increase in rate. In a number of cases urinary excretion was limited. Fever was uncommon and never exceeded 102° F. (fig. 6). It was recorded in twelve cases : in three it was attributable to urinary infection and in four as a sequel to convulsions. In the remaining five cases the temperature rose on the second or third day and fell within forty-eight hours without increase in fluid intake.

A return of symptoms after a quiescent period varying in length from three to eight days was noted in six infants (fig. 7). In two instances convulsions occurred when the infant was put to the breast for the first time, in one after ' lifting ' of the infant and in another during bathing. Constipation appeared to be an aggravating factor in a fourth case.

Death occurred suddenly in the three cases in which evidence of recurrence of haemorrhage was present at autopsy : in others it was preceded by a period of semi-coma in which the eyes became glazed, the breathing stertorous and the body cold. Thirty-four infants died during the first six days of life ; the longest duration of life was nineteen days. In the eight infants living more than one week death followed a recurrence of haemorrhage in two, and in one the clinical course suggested that gross bleeding did not occur until after the

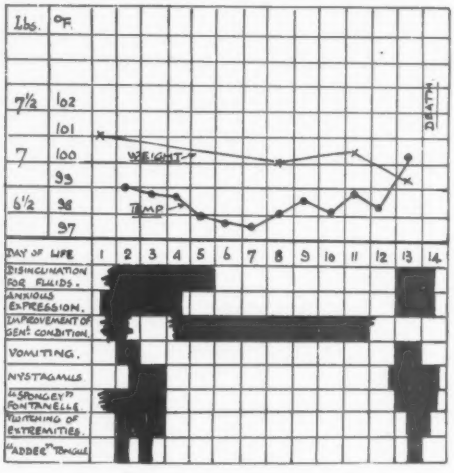

FIG. 7.—Case No. 198. Subdural haemorrhage in a first child delivered with forceps after previous instrumental rotation of the head. Symptoms of intracranial trauma were present on the day of birth ; persisted for three days ; were followed by a week of progressive improvement and recurred suddenly on the thirteenth day, death occurring within thirty-six hours. At autopsy a recent massive, supratentorial haemorrhage was found in association with extensive, old, changed, blood clot (see also fig. 3).

first week. Death was due to causes other than intracranial haemorrhage in five cases and extensive pulmonary lesions (pneumonia or haemorrhage) were present in seventeen infants.

Subarachnoid haemorrhage

Extensive haemorrhage into the subarachnoid space was found at autopsy in thirty-six infants, of whom seven were born at term and twenty-nine were premature. Delivery was spontaneous in thirty cases including five breech presentations. It was instrumental in the case of three, and in the remaining three cases Caesarean section was performed. The series included eighteen first pregnancies. A history of pre-eclamptic toxaemia was obtained in connexion with five mothers. Hydramnios was a feature of three, threatened abortion of two and hyperemesis of one pregnancy. Other morbid antenatal conditions recorded in connection with the mothers included chronic cardiac disease in three, gastric ulcer in one and acute pyelitis in another.

Pathological findings.—Bleeding resulted from capillary oozing and not from any localized intracranial injury. The haemorrhage varied in extent and distribution. In some cases it was most marked over the vertex ; more

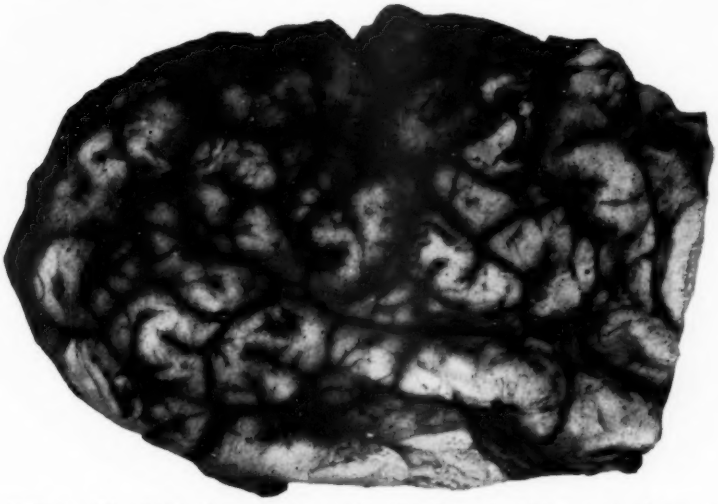

FIG. 8.—Case No. 140. Naked-eye appearance of subarachnoid haemorrhage. The photograph was taken in a preserved specimen and the appearance of the haemorrhage is less striking than that seen at autopsy.

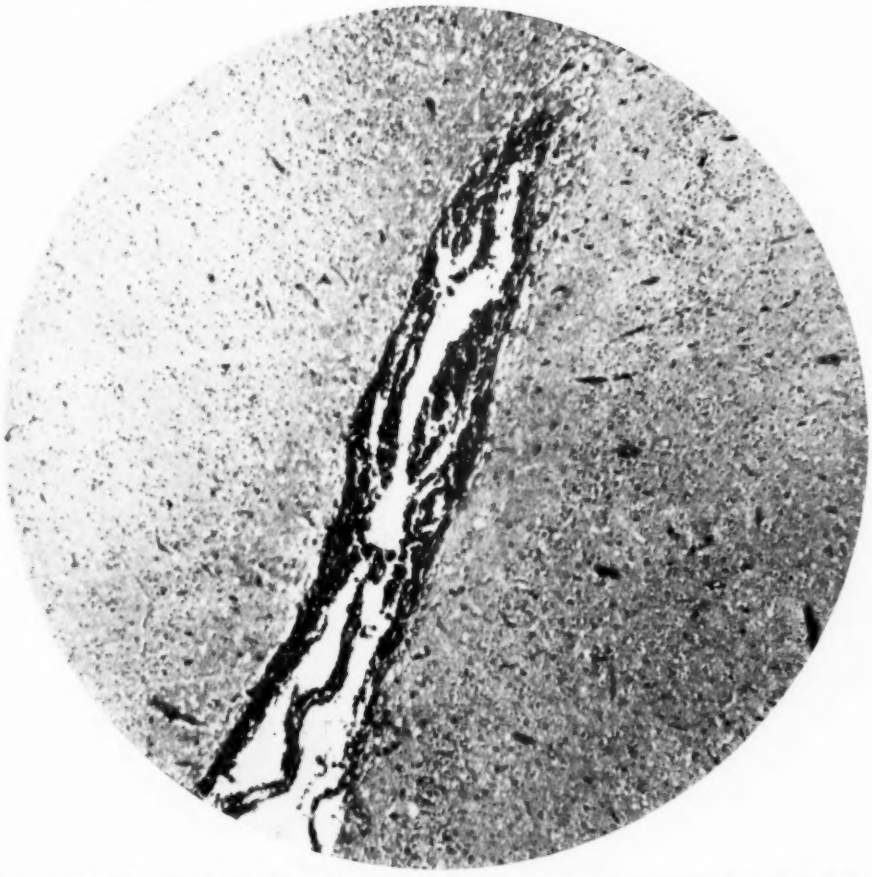

FIG. 9.—Case No. 11. Extensive subarachnoid haemorrhage associated with localized patches of early softening of the superficial cortical layers and slight oedema of the cerebral substance. There is considerable distension of, but no haemorrhage from the larger veins. An excess of large endothelial macrophages was present in the meninges indicative of early active phagocytosis of extravasated red blood cells.

commonly it was related to the occipital and posterior parietal surfaces ; usually bilateral, it was limited to one cerebral hemisphere in a few cases.

The picture of severe leptomeningeal haemorrhage was characteristic. Cerebro-spinal fluid was present in excess and the brain was completely enclosed within a reddish-yellow layer of jelly-like consistence (fig. 8). The meninges were sodden and congested, and floated on a heavily blood-stained fluid separating them from the brain substance. Specimens were difficult to preserve :

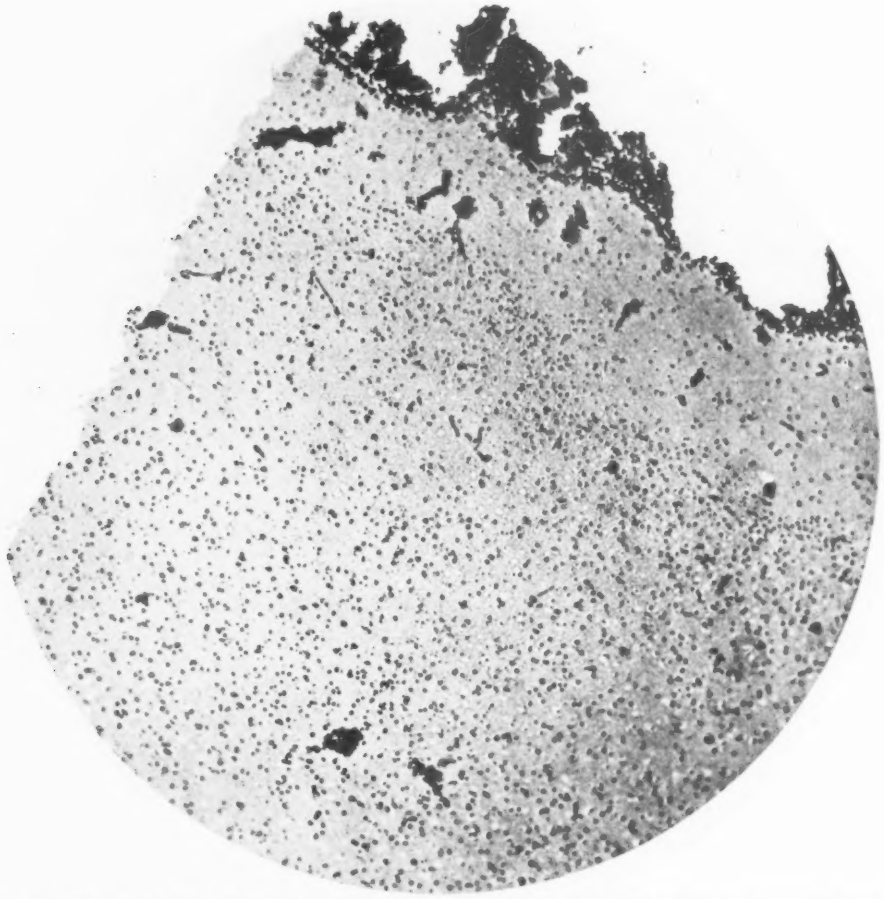

FIG. 10.—Case No. 35. Extensive subarachnoid haemorrhage. The pia arachnoid has been removed. There are a number of minute cortical haemorrhages which have originated from capillaries or small venules and of which the majority are situated in the superficial layers of the cortex.

the gentlest handling usually denuded the brain of its jelly-like covering, and specimens in which this did not occur failed to retain their characteristic colour. Fig. 9 and 10 show the microscopic appearance of subarachnoid haemorrhage. There is slight venous congestion of the brain substance and early softening near the surface. In other cases the brain substance was slightly oedematous and there were minute haemorrhages in the cortex.

Atelectasis and evidence of asphyxia were constant findings : haemorrhage into the lungs or pneumonia or both were present in seventeen infants and other

haemorrhages found included bleeding into the intestinal wall (three), into serous sacs (two) and into the suprarenal glands (two).

Clinical observations.—The condition of all these infants was unsatisfactory at birth ; in eighteen there was no improvement and death occurred within forty-eight hours. The extent of improvement occurring in those living for a longer period was variable. Persistent absence of all desire for fluids was noteworthy. Irrespective of the maturity of the infant the weight showed an initial fall of normal proportion, but usually failed to show any subsequent gain. Where a gain of a few ounces did take place death was preceded by a period of arrested weight progress or actual loss of weight (figs. 11 and 12).

Evidence of intracranial trouble was liable to be obscured by physical frailty. It was detected in only 50 per cent. of cases. Convulsions occurred in one infant. Slight twitching of short duration and involving the hands and face was seen in seven cases. Failure to observe involvement of the lower limbs is

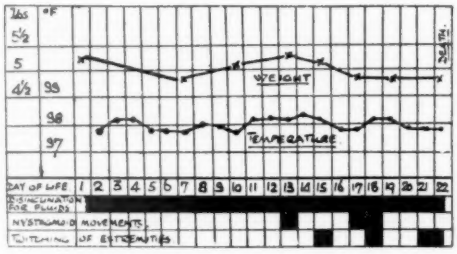

FIG. 11.—Case No. 7. Subarachnoid haemorrhage in a premature infant. Symptoms were preceded by fall in weight ; pustules and stomatitis were a feature during the last ten days of life. Pneumonia was present at autopsy. The mother suffered from toxaemic symptoms.

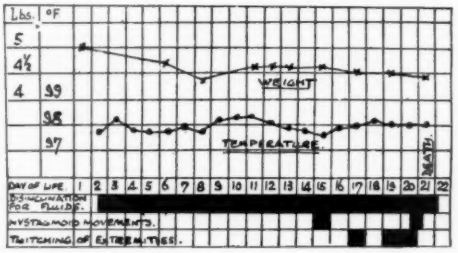

FIG. 12.—Case No. 217. Subarachnoid haemorrhage in a premature infant. Symptoms were preceded by an arrest in weight progress. The mother was an eclamptic.

probably attributable to the fact that twitching had ceased before the legs were exposed for examination. It was not found possible to correlate the localization of the twitching and the distribution of the haemorrhage, but it was noted that convulsive movements occurred only in association with extensive bleeding. Small cortical haemorrhages were present in four cases in which peripheral twitching movements were seen and in the one case associated with convulsions ; they were also present in cases showing neither twitching nor convulsions.

Restless ocular movements were seen in twelve infants. They were a constant accompaniment of twitching of the extremities : in four cases they took the form of true nystagmus. Inequality of the pupils and conjunctival haemorrhages were recorded in several cases; rapid protrusion of the tongue, spastic flexion of the limbs and retinal haemorrhages were rare findings. Examination of the fontanelle proved of little value : it was never tense and only occasionally felt abnormally 'spongey.' There was nothing characteristic about the facies.

Vomiting on isolated occasions was a feature in seven cases : in two of these it appeared to be the result of swallowing meconium, and in two the vomitus contained blood derived from congested gastric mucosa. Colour was poor throughout life and became increasingly cyanotic : improvement followed the administration of oxygen in a few cases in which pulmonary lesions were present, but in general the cyanosis was less subject to variations than in other forms of cerebral haemorrhage. Fever was noted in only five infants ; it

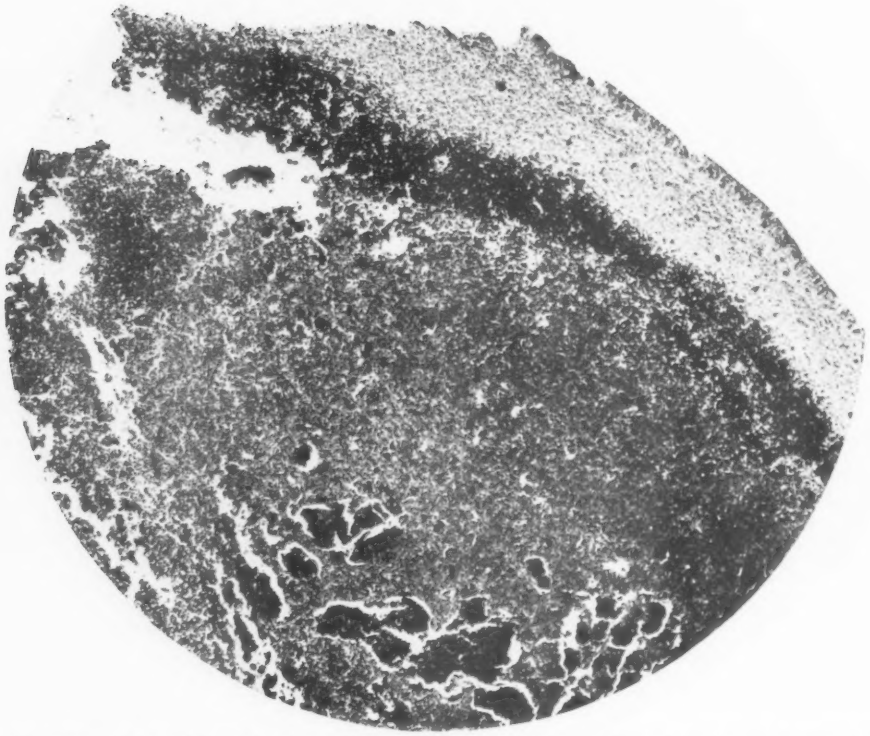

FIG. 13.—Case No. 208. Massive bleeding into the brain substance under the ependymal surface of the ventricle in a case of intraventricular haemorrhage. The source of the bleeding is not shown, but at autopsy haemorrhage was seen to have occurred from superficial veins in the ventricular walls and from veins in the choroid plexus.

was terminal in each case and associated with an unusually severe loss in weight. The highest recorded temperature was 103° F.

Intraventricular haemorrhage

There were twenty-two cases of intraventricular haemorrhage : in nineteen the infant was premature, in one full time, and in two post-mature at birth. Delivery was spontaneous in eighteen (including two breech presentations) and instrumental in three cases. Caesarean section was performed in one case. There were twelve first pregnancies. Six mothers gave a history of eclamptic

fits and seven of pre-eclamptic toxaemia. Two mothers received antenatal treatment for syphilis and one for gonoccocal infection. Of four other mothers with morbid conditions during the latter half of pregnancy one suffered from a profuse leucorrhoeal discharge, another was grossly anaemic, a third had repeated carbuncles and a fourth cellulitis of the leg.

Pathological findings.—Intraventricular haemorrhage was associated with capillary oozing of limited extent into the subarachnoid space in four, and

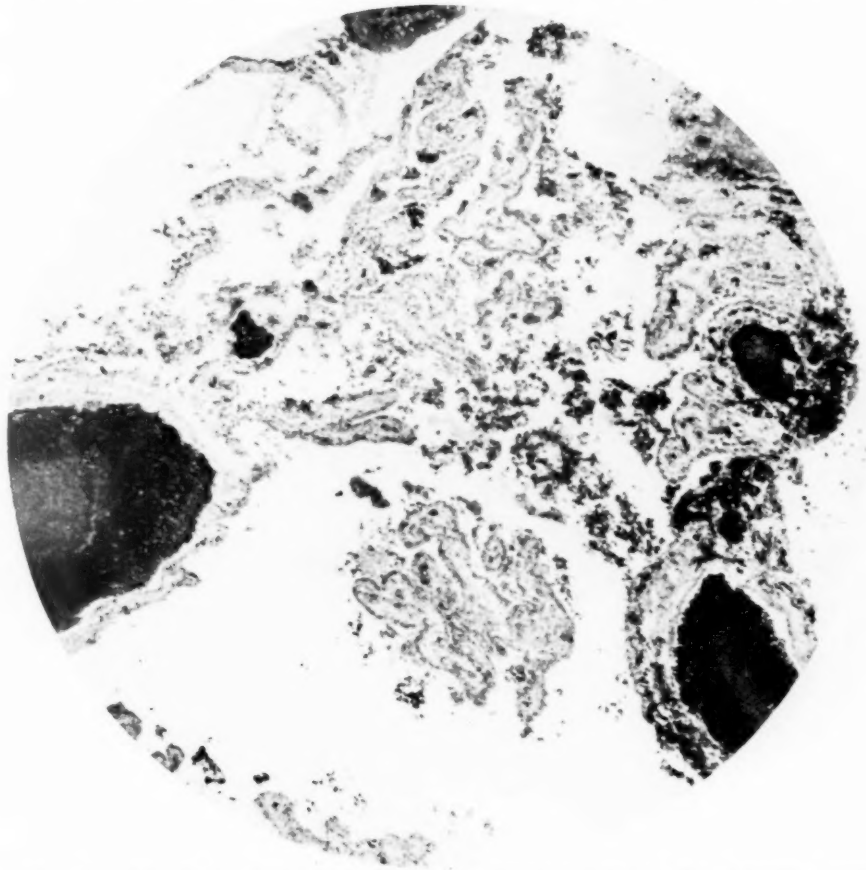

FIG. 14.—Case No. 132. Recent thrombosis of numerous veins of the choroid plexus in a case of intraventricular haemorrhage. Haemorrhage has occurred in and about the plexus.

with isolated minute cortical haemorrhages in three cases. Massive intraventricular bleeding resulted in increase in the size of the brain and marked flattening of the convolutions over the vertex. The source of the haemorrhage was the veins of the choroid plexus in fourteen, and the superficial veins in the ventricular wall in two cases (fig. 13). Bleeding occurred from both these sites in four instances and in two its origin was not found. Haemorrhage followed acute engorgement of the veins or occurred as a sequel to thrombosis (fig. 14). In cases included in this series thrombosis was unaccompanied by evidence of infection.

Haemorrhage was invariably gross. Blood was found throughout the entire ventricular system in several cases (fig. 15). It was usually present only in the lateral ventricles and occasionally was confined to the posterior horns, or was limited to one side. In a number of cases the ventricles were filled with blood clot without associated damage to the brain substance. Gross destruction of brain tissue was present in seven cases : in three of these the haemorrhage was visible through a thin layer of cortex ; in four it had ruptured through an occipital pole into the subdural space (fig. 16).

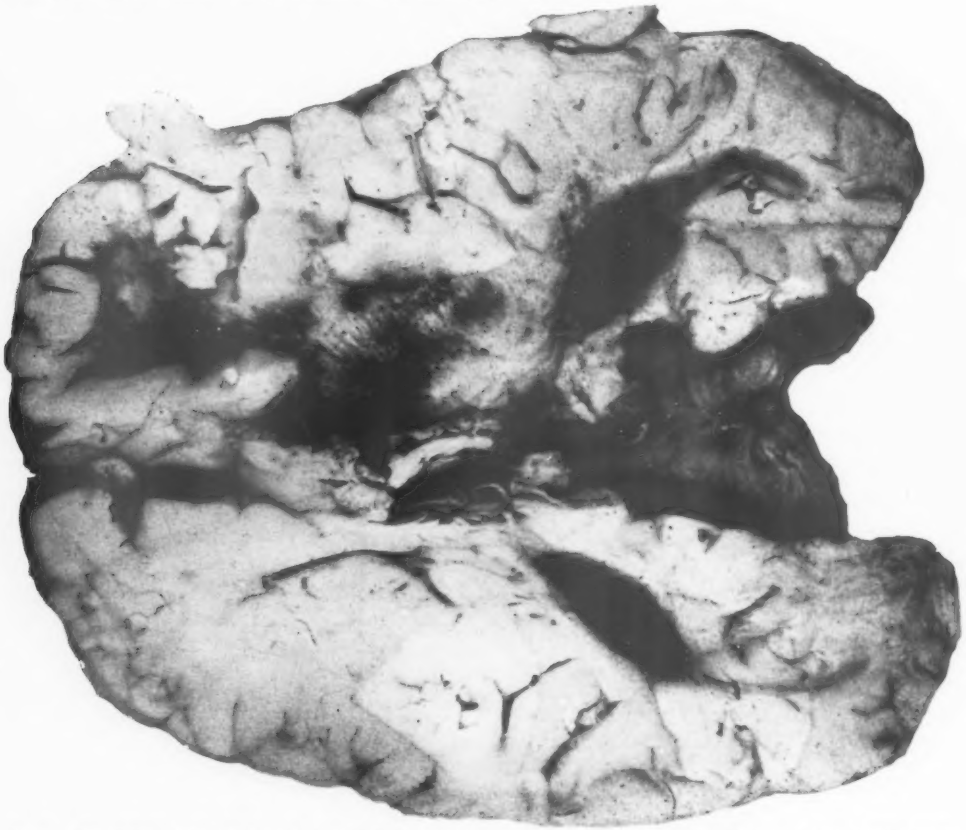

FIG. 15.—Case No. 111. Intraventricular haemorrhage with destruction of the brain substance. Blood is present throughout the ventricular system and both posterior horns are completely filled with blood clot.

Atelectasis was a common finding : pneumonia or intrapulmonary haemorrhage—both were present in thirteen and venous thrombosis in the kidneys in one case. Haemorrhages other than cerebral or pulmonary were a feature of six cases : they included bleeding into serous cavities (three), into the intestinal wall (three) and into suprarenal glands (two).

Clinical observations.—There was an absence of clinical evidence pointing to intracranial haemorrhage in six cases. All six infants were distressed at birth and died within twelve hours of delivery : in each instance bleeding had arisen from the choroid plexus, was severe, but had not resulted in destruction of brain substance. The remaining sixteen infants presented a striking clinical

picture (figs. 17 and 18). They were all premature. During the first week of life they showed no desire for fluids and their weight failed to increase after an initial physiological loss. Symptoms developed with dramatic suddenness : their calamitous significance was immediately apparent in the complete change in the general condition.

Onset of the condition occurred at any time during the first three weeks of life, death invariably occurring within forty-eight to sixty hours. A cry frequently coincided with the onset. The cry was unmistakable. Its piercing

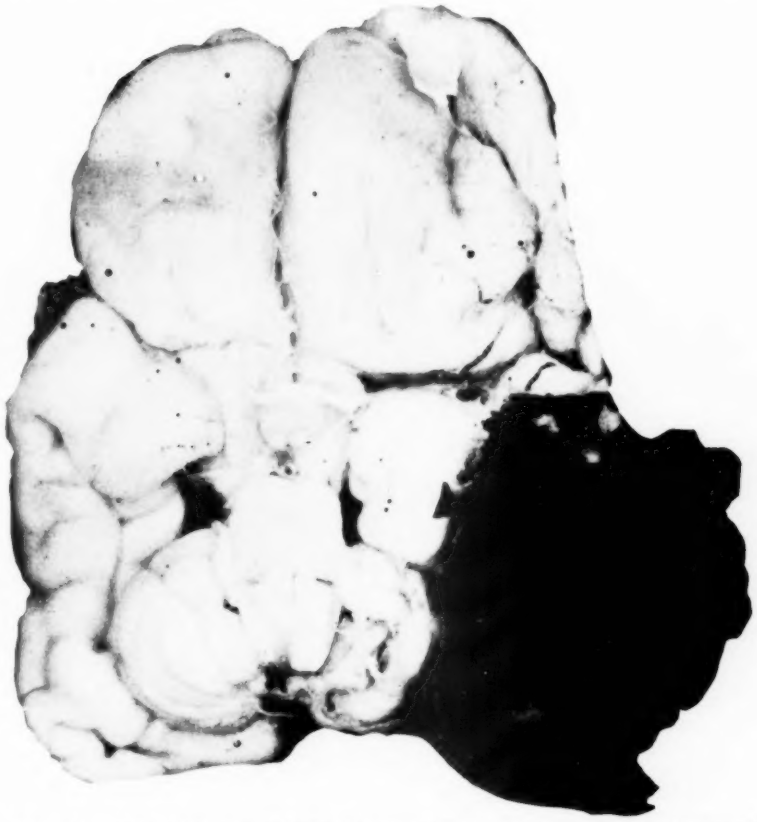

FIG. 16.—Case No. 246. Intraventricular haemorrhage. View of the under-surface of the brain in a case in which massive haemorrhage into the ventricles ruptured through the left occipital pole. There was extensive destruction of brain substance. The clot shown in the figure represents only a portion of a large clot of which the remainder occupied the cavity enclosed by undamaged and partially damaged brain substance.

shrillness and agonized note were typical. The facial expression of ' torture ' was equally characteristic. The eyes protruded, the pupils were dilated and the conjunctivae injected. Coarse nystagmus was present in every case. There were constant head rolling and agitated movements of the arms ; the trunk was rigid, the hands were fiercely clenched and the legs drawn up on the abdomen. The colour was ashen grey, and respirations rapid and panting. Attacks of this nature occurred at intervals until death ; between attacks the infants were left in a state of complete physical and mental exhaustion. Opisthotonos was seen once and head retraction on several occasions. A tense, bulging

fontanelle, sometimes sufficiently prominent to be seen, was characteristic. Gross twitching of the face and limbs were present in every case and generalized convulsions in the majority : abnormally brisk during attacks, tendon reflexes were diminished in the intervals between them. There was darting tongue protrusion in eight cases. Vomiting was only noted in three infants, but in each it was violent and preceded other clinical signs. Temperatures exceeding 107° F. were recorded in five cases and over 103° F. in seven others. Death

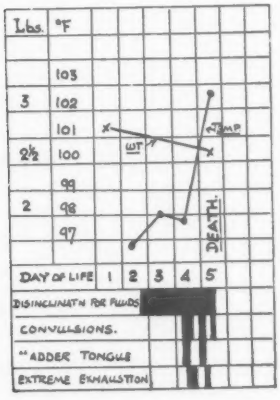

FIG. 17.—Case No. 271. Intraventricular haemorrhage occurring in a premature infant in the first week of life and characterized by the sudden onset of symptoms, a rapid course and terminal pyrexia. The mother suffered from pre-eclamptic toxaemia.

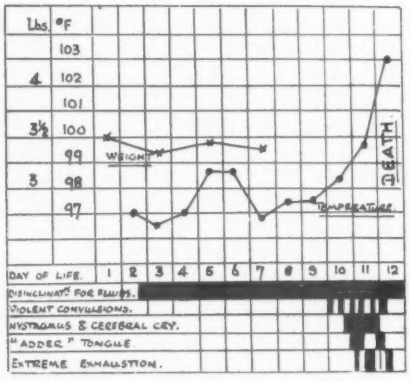

FIG. 18.—Case No. 19. Intraventricular haemorrhage occurring in a premature infant in the second week of life. Haemorrhage was preceded by a period during which weight progress was interrupted, and resulted in the sudden onset of violent symptoms and terminal pyrexia. Extensive pneumonia was present at autopsy. The mother was a pre-eclamptic.

was usually preceded by increasing cyanosis and sometimes by coma. In the majority of cases it occurred suddenly following a recurrence of generalized convulsions.

Haemorrhage into the brain substance

Six cases are included in this group. In them, individual haemorrhages were limited in extent but numerous, and distributed throughout the brain substance. Cases described under subarachnoid and intraventricular bleeding associated with isolated cortical haemorrhages (pp. 96 and 101) are not included. The six infants were born at term after normal pregnancies, five of which were first pregnancies. Delivery was spontaneous in two and instrumental in four cases. The instrumental deliveries included one in which forceps had been applied after manual rotation of the head, and another in which rotation had been secured with the aid of forceps. Labour was prolonged in each case.

Pathological findings.—In all six cases the naked-eye appearance of the brain and the microscopic findings were the same. The brain was swollen and the convolutions over the vertex flattened ; it had a uniformly red appearance

as a result of congestion of dural and leptomeningeal vessels. The cut surface of cerebrum, cerebellum and mid-brain showed similar, severe congestion ; the cortical regions were a deep reddish-purple colour ; the medullary portions were studded and streaked by distended vessels and bleeding points.

Microscopically there was generalized congestion of veins and capillaries with related perivascular haemorrhages (fig. 19). The brain substance was

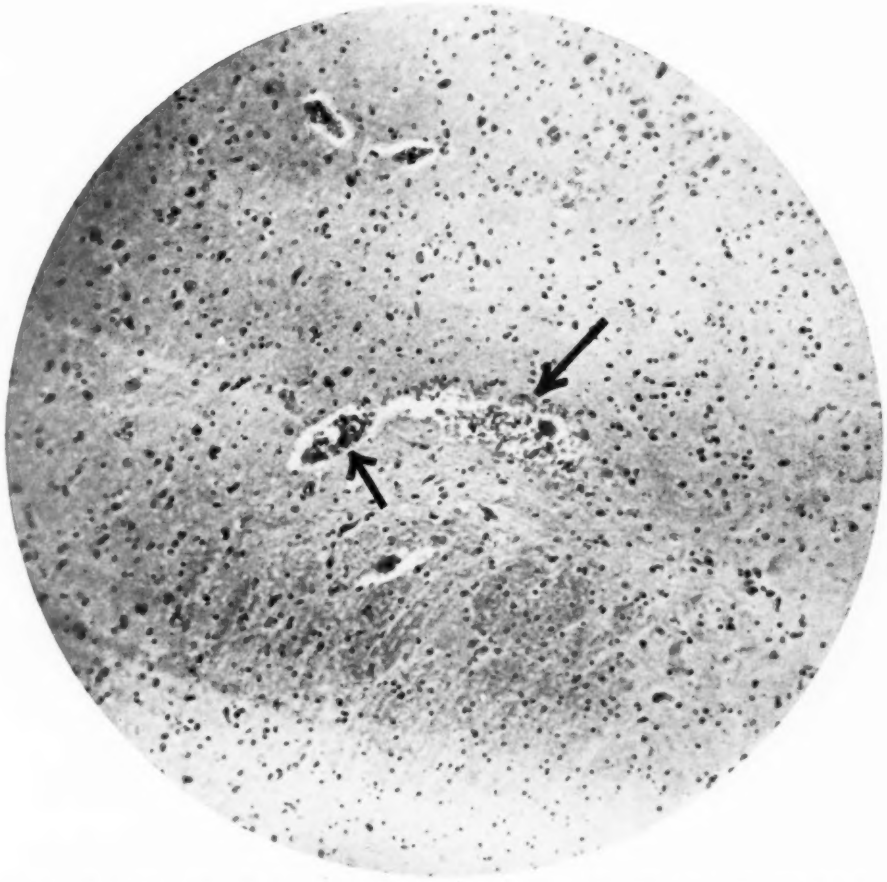

FIG. 19.—Case No. 75. Perivascular haemorrhages (marked with arrows) associated with generalized capillary and venous congestion in the cerebrum of a case of haemorrhage into the brain substance. There is slight oedema of the brain substance. At autopsy the external and cut surfaces of the brain and mid-brain were bright red in colour. Both medulla and cortex were stippled with discrete bleeding points. The brain was swollen, the convolutions flattened, the meninges congested and the brain substance soft.

slightly oedematous (fig. 20). Haemorrhages were numerous and had occurred in all parts of the brain, but were greater in number in the cerebrum than in cerebellum or mid-brain. The cord was examined in four of the cases : there were no pathological changes apart from slight congestion of the related meninges.

Extensive atelectasis was a feature of all six cases and was associated with early pneumonia in two.

Clinical observations (figs. 22, 23, and 24).—All the six children were distressed at birth, but their condition did not appear critical. They improved slowly, but remained unnaturally quiet and inactive ; did not cry for fluids but swallowed when spoon or pipette was used ; and were left undisturbed by examinations. Their colour was good, but body temperature was maintained with difficulty ; pulse and respirations were slow and tendon reflexes diminished. A striking feature of this phase was its duration : it persisted unchanged for six to ten days. It was followed by a period lasting several days of great mental

FIG. 20.—Case No. 286. Perivascular haemorrhages and generalized congestion in and oedema of the brain in a case of intracerebral haemorrhage. The macroscopic appearance of the brain resembled that described in connexion with fig. 19.

agitation and increasing physical weakness. The eyes were constantly open. They became more sunken and developed continuous, restless movements in all directions, but never true nystagmus. Later a cry was heard. At first peevish and at long intervals, it became more frequent and more typically cerebral ; it was accompanied by head rolling. There was slight fullness of the fontanelle in two cases. Twitching of all extremities and both sides of the face was seen in three infants.

In the early stages the facial expression was sullen and frowning. Simultaneously with the occurrence of a cry of pain and with restless movements of the

eyes it became one of intense fear. Later, as general weakness increased, the expression became strangely vague and distant. In connection with two infants it prompted the remark from the sister-in-charge, ' This child is going to be mental.' The facies were striking and reminded the writer of those seen occasionally in fatal cases of acute encephalitis in young children.

The weight of infants in this group fell rapidly and without interruption from the day of birth until death. A daily loss of 8 oz. was not uncommon. Occasional vomiting occurred in all six cases. The colour became grey and Cheyne-Stokes breathing developed in three infants. Slight spasticity of the

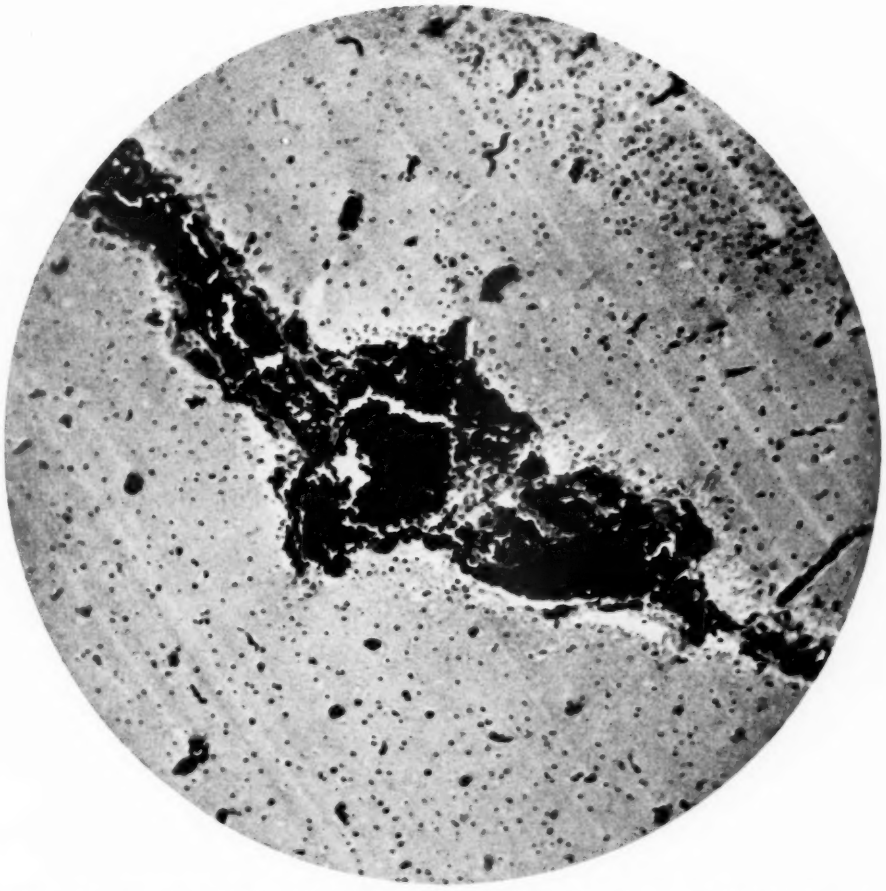

FIG. 21.—Case No. 286. High-power magnification of perivascular haemorrhage.

limbs and inability to swallow were late features : retinal haemorrhages were detected in three cases.

Great exhaustion followed a period of mental agitation. Death came gradually and followed a state of coma lasting for a period of about two days, during which time breathing was stertorous, cyanosis increased, and the temperature rose (101° F. to 103° F.).

Discussion

Trauma to the child during birth has been described by von Reuss (1935) as inevitable even under the most favourable conditions. Trauma may be ante-natal in origin and may arise from post-natal developments. Irrespective of the time of its occurrence in relation to delivery, the extent, nature and localization of trauma in the new-born child largely determine the prospects of survival in the neo-natal period.

Bland (1934) described intracranial lesions as the most serious form of trauma to which a new-born child is subject and as the most frequent finding at autopsy.

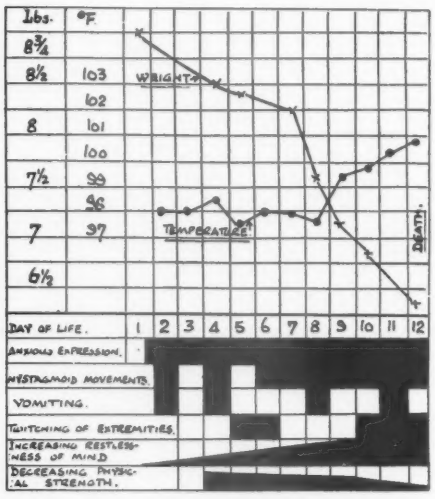

FIG. 22.—Case No. 286. Multiple perivascular haemorrhages in the brain substance of a large first child. The mother was aged fifteen years and delivery was instrumental. Symptoms were present from birth and were associated with increasing restlessness of mind, extreme physical weakness and a precipitous fall in weight. At autopsy haemorrhages were found throughout the brain and mid-brain. (See also fig. 20 and 21.)

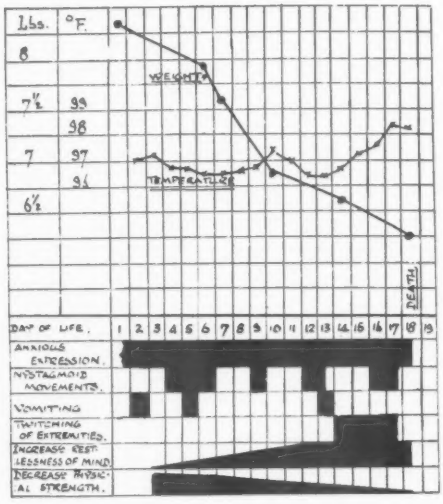

FIG. 23.—Case No. 208. Multiple perivascular haemorrhages in the brain substance of a large first child. The mother was aged forty-four years and delivery instrumental. Clinical and pathological findings resembled those in Case No. 286 (fig. 22). See also fig. 13.

They were present in eighteen of thirty-six cases recorded by Warwick (1919); in fifteen of twenty-eight cases published by Capon (1922); and in 130 of 290 consecutive cases of neo-natal death examined post mortem by the writer.

Haemorrhage is the most common accompaniment of intracranial injury. It may result from or contribute to damage of the brain substance and meninges, and it may be present in the absence of macroscopical evidence of injury to these structures.

Litchfield and Girvan (1934) and Ehrenfest (1922) describe the occurrence of haemorrhage between two opposed dural layers without damage to the dural surfaces. Cruickshank (1930), von Reuss (1930) and others have drawn attention to the tearing of sinuses and vessels, frequently in association with injury to the dural septa as a cause of haemorrhage. Capillary oozing from the

meninges was found to be common by Cruickshank (1930) in an investigation of neo-natal death based upon 800 autopsies. He describes it as usually occurring in association with evidences of asphyxia and as a not uncommon finding in premature infants in many of whom the intracranial contents are characterized by oedema. Described variously as leptomeningeal or sub-arachnoid, haemorrhage resulting from capillary oozing has been referred to by von Reuss (1935), Schwartz (1922), Griffiths and Mitchell (1933), Hendler (1935), Ehrenfest (1922) and others.

Haemorrhage into the cerebral ventricles has been attributed to capillary haemorrhage, asphyxial congestion, and injury and diseases of the mother and infant by Cruickshank (1930), and to rupture of vessels of the choroid plexus by Litchfield and Girvan (1934). Hemsath (1934) records the findings at autopsies on nineteen new-born infants in whom intraventricular haemorrhage was found. He was unable to determine the source of the haemorrhage in six, but considered that bleeding into the ventricles was due to sub-ependymal

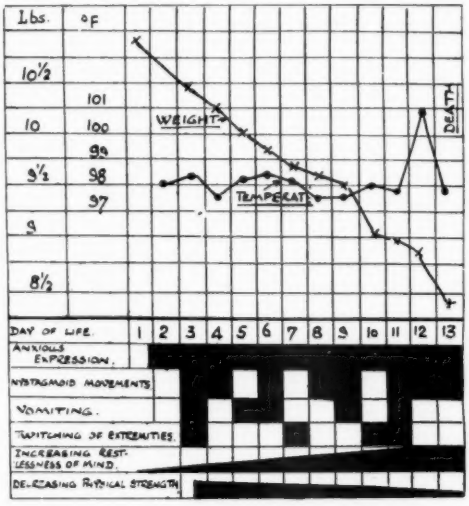

FIG. 24.—Case No. 75. Multiple perivascular haemorrhages in the brain substance of the fourth child of a mother aged twenty-nine years. Delivery was instrumental. The mother showed signs of uterine inertia. Clinical and pathological findings resembled those in connexion with Cases 208 and 286 (fig. 22 and 23).

haemorrhage in seven, to haemorrhage from the choroid plexus in two and to a combination of bleeding from the choroid plexus and from sub-ependymal vessels in four cases. He describes the presence of blood in the ventricles of one case as being part of a massive intracerebral haemorrhage. Von Reuss (1920), Ylppo (1919), Browne (1922), Hendler (1935), Litchfield (1934), Cruickshank (1930) and Hemsath (1934) are agreed that the condition almost invariably occurs in premature infants.

The importance of haemorrhage into the brain substance has been emphasized by Schwartz (1922), and Hemsath and Canavan (1932) have drawn attention to the association of subpial haemorrhages with small extravasations into the brain. They found intracerebral haemorrhages at thirty-four of fifty-three autopsies and considered them to be the cause of death in twelve cases. Ford (1927) is of the opinion that multiple petechial haemorrhages in the brain and meninges are found in all forms of asphyxia. Von Haan (1934) found macroscopical evidence of haemorrhage into the brain substance in four of fifty cases examined post mortem. Couvelaire (1903) records the presence of haemorrhage in the cortex of two and in the central white matter and basal ganglia of three cases. Hendler (1935) finds haemorrhages in the

brain substance at autopsy in 65 per cent. of full-time and 95 per cent. of premature infants. He describes the haemorrhages as usually originating from the vein of Galen, states that usually they can only be recognized microscopically, and considers that they are more of a theoretical than a practical interest. Crothers (1923) is in agreement with the view of Hemsath and Canavan (1932) that significance attaches to haemorrhages in the region of the medulla as a cause of asphyxia. In contrast Warwick (1921) reports not having found any evidence of primary haemorrhage into the brain substance. Cruickshank (1930) expresses doubt as to the supposed frequency of small areas of haemorrhage in the brain substance, but allows of their occurrence in unusual circumstances.

Cruickshank (1930) divides intracranial bleeding into meningeal capillary oozing, traumatic intradural bleeding from the choroid plexus and bleeding associated with disease of the mother or of the infant. Munro (1928) discusses haemorrhages according to whether they are the result of trauma or asphyxia, or are a manifestation of haemorrhagic disease. Other workers, including Hendler (1935) and von Haan (1934), adopt a classification more strictly dependent upon the anatomical location of the bleeding, and they group haemorrhages according to whether their distribution is subpial, subarachnoid, subdural, intraventricular or intracerebral. Ehrenfest (1929) differentiates subdural haemorrhages according to whether they are supratentorial or infratentorial, and haemorrhages into the brain according to whether they are diffuse or circumscribed. A similar classification is adopted by von Reuss (1920) for cases of intracerebral haemorrhage. He groups cases with symptoms simulating those of intracranial haemorrhage during life and showing only hyperamia and oedema of the brain and meninges at autopsy under the separate heading of ' contusio cerebri.' Munro and Eustis (1922) distinguished traumatic haemorrhage due to foetal distress from that arising from asphyxia.

The exact relationship between asphyxia and intracranial haemorrhage is discussed at length by Cruickshank (1930). He attaches considerable importance to asphyxia as a factor in causing capillary oozing from the meninges and from the choroid plexus in favouring a rupture of vessels related to dural tears and in accentuating the haemorrhage from traumatized areas. Discussing cranial haemorrhages von Reuss (1920) states that their severity is frequently determined by the degree and persistence of associated asphyxial stasis. Serbin (1928) and Capon (1922) are among others who have drawn attention to the importance of asphyxia in this connexion. Bland (1934), on the other hand, considers that asphyxia is a symptom rather than a cause of intracranial haemorrhage. Ford (1926) is of the opinion that asphyxia is not a common cause of cerebral birth injury and failed to produce brain lesions in animals by experimental asphyxia. The etiology of intracranial haemorrhage has been the subject of many investigations but not all recorded results deal separately with the different types of haemorrhage which may occur. Instrumental delivery ; difficult, prolonged or too-rapid labour ; abnormal presentation ; manoeuvres in rescuscitation ; and prematurity of the infant are among the factors most frequently quoted as favouring intracranial haemorrhage. In this connexion special reference is made to podalic version by Burpee (1933), to the peculiar risks of a first, and particularly a male first-born child by Gland (1934) and to the obstetrical use of pituitrin by Nattrass (1934). Warwick (39) and Foote (14) consider that in many cases intracranial bleeding results from a haemorrhagic diathesis. Sharpe and Maclaire (1925*a* and *b*) and Cruickshank (1930) hold the view that a haemorrhagic diathesis seldom explains intracranial bleeding. Among haematological factors suggested as favouring haemorrhage in the new-born are biochemical changes by Bland (1934), physiological delay in the coagulation time by Griffiths and Mitchell (1933) and a deficiency of prothrombin together with a qualitative defect of blood platelets by Heffernan (1932).

Subarachnoid haemorrhages are described by Ehrenfest (1922) as occurring most commonly in premature infants and as being usually associated with syphilis or haemorrhagic disease.

Bleeding into the ventricles is believed by Cruickshank (1930) to be the usual form assumed by haemorrhage attributable to disease of the infant or the mother. The occurrence of intraventricular haemorrhage in each of triplets is quoted by Hemsath (1934) in support of his view that constitutional factors are of importance in intraventricular haemorrhage.

The symptomatology of intracranial haemorrhage in the new-born has been the subject of study by many workers. Von Reuss (1935) draws attention to the difficulties attached to the clinical differentiation of asphyxial from traumatic intracranial haemorrhage in the asphyxiated new-born child. Not all recorded observations take account of the underlying pathology. Few studies attempt to correlate symptoms with the type of haemorrhage present, and the majority accept a somewhat broad classification of symptoms. Thus Griffiths and Mitchell (1933) group symptoms according to whether they indicate increased intracranial pressure or increased nervous irritability. A somewhat similar classification is adopted by Levinson (1935), who groups symptoms into those which are 'irritative,' those which are 'somnolent' and those which are both irritative and somnolent. Santamarina (1934) differentiates symptoms indicative of supratentorial haemorrhage from those suggestive of infratentorial haemorrhage. Cruickshank (1930) adopts a similar classification in the case of symptoms arising from gross intracranial bleeding. Ott (1934) is of the opinion that recognizable symptoms may be classified according as they arise from cortical irritation or from haemorrhage in the region of the medulla.

Von Reuss (1920) contrasts the symptomatology of supratentorial, as opposed to infratentorial, subdural haemorrhage ; stresses the resemblance of symptoms arising from simple 'contusio cerebri' and those from subdural haemorrhage ; states that intraventricular simulates infratentorial haemorrhage, and remarks upon the absence of recorded clinical observations in cases of intracerebral bleeding. Discussing supratentorial haemorrhage he states that, while in a number of cases death occurs shortly after birth, in others improvement precedes symptoms of cerebral pressure. He describes convulsions as the most characteristic and most important symptom, as being frequently provoked by external stimuli, and as varying considerably in severity. He states that death usually takes place between the fifth and eighth day, is preceded by a period of paralysis characterized by an absence of reflexes and is frequently the result of aspiration pneumonia.

Infratentorial haemorrhage is described by von Reuss as differing from supratentorial bleeding in an absence of painful cries, restlessness and tension of the fontanelle in the early stages of the condition and in the presence during the later stages of marked cyanotic spasms, nuchal rigidity, opisthotonos, penile erection and spasms of the limbs.

Among clinical findings recorded by other workers it is stated by Browne (1922) that intraventricular haemorrhage is rarely indicated by clinical signs and usually occurs in weakly premature infants. Santamarina (1934) considers bradycardia to be characteristic of infratentorial haemorrhage and Griffiths and Mitchell (1933) are of the opinion that intracranial haemorrhage results in irregularity of the pulse. Convulsions are described by Griffiths and Mitchell (1933) as relatively common in the new-born and as of less value in the diagnosis of intracranial haemorrhage than paralytic symptoms. General convulsions are stated by Capon (1922) to be of particular significance when seen soon after birth and to terminate usually before the third day of life. Capon (1922) and Levinson (1935) are in agreement that external haemorrhages from the nose and pharynx are common, but disagree in that the latter records that the temperature is not elevated, whereas Capon considers that slight pyrexia

indicates progressive bleeding within the cranium. Attention has been drawn to the presence of retinal haemorrhages, but Fleming and Morton (1930) consider that they occur in a proportion of healthy new-born children and are of no value in diagnosis. The pained expression of infants with cerebral haemorrhage is remarked upon by Levinson (1935), and Shannon (1934) attached considerable importance to tetany, which he describes as part of a syndrome associated with a tendency to generalized oedema and oedema of the brain. Shannon (1934) is of the opinion that slowness of pulse and respirations, cyanotic attacks, projectile vomiting, tension without protrusion of the fontanelle and other cerebral symptoms are to be attributed to oedema of the brain and not to cerebral haemorrhage.

The present series

The different types of intracranial haemorrhage found are given in table 1. Of the 126 cases included in the investigation, subdural haemorrhage was present in forty-nine per cent., subarachnoid haemorrhage in twenty-nine, intraventricular haemorrhage in seventeen and haemorrhage into the brain substance in five per cent. While the etiology of the different forms of intracranial bleeding does not come within the scope of this paper, discussion would be incomplete without reference to certain factors which, although related primarily to causation, are of importance in diagnosis. Tables 2–9 deal with these factors. They indicate that first children predominated in the entire series and in each type of haemorrhage, but that the preponderance was most marked in cases of subdural haemorrhage (table 2) ; that the majority of cases with subdural bleeding associated with tentorial tears and all the cases with haemorrhage into the brain substance were born at term, and that in contrast twenty-nine of thirty-six cases of subarachnoid haemorrhage and nineteen of twenty-two cases of intraventricular haemorrhage were premature (table 3) ; that instrumental delivery was a feature of two-thirds of the cases with intracerebral and with subdural haemorrhage in association with tentorial tears, but of only six in a total of fifty-eight cases with subarachnoid or intraventricular haemorrhage (table 4) ; that a history of debility, toxaemia or infection of the mother during pregnancy was obtained in connexion with sixteen of thirty-six cases of subarachnoid haemorrhage and twenty of twenty-two cases of intraventricular haemorrhage (table 6); and that intracranial bleeding was associated with other morbid conditions and in particular with pulmonary lesions in a large number of cases (table 7).

TABLE 1

INTRACRANIAL FINDINGS AT 126 AUTOPSIES

Subdural haemorrhage arising from tentorial tears	42
Subdural haemorrhage arising from lesions other than tentorial tears ..	20
Subarachnoid haemorrhage	36
Intraventricular haemorrhage	22
Haemorrhage into brain substance	6
	126

(Limited subarachnoid haemorrhage was present in addition, in six cases of subdural haemorrhage, five of intraventricular haemorrhage and in two cases of haemorrhage into the brain substance.)

TABLE 2

THE NUMBER OF PREGNANCY IN RELATION TO THE TYPE OF HAEMORRHAGE

TYPE OF INTRACRANIAL HAEMORRHAGE	NUMBER OF PREGNANCY											TOTAL NO. INFANTS
	1	2	3	4	5	6	7	8	9	10	11	
Subdural (tentorial tears)	31	2	6	2	—	—	—	—	1	—	—	42
Subdural (not associated with tentorial tears) ..	13	5	—	1	—	—	—	—	—	1	—	20
Subarachnoid	18	5	7	2	3	1	—	—	—	—	—	36
Intraventricular ..	12	2	3	1	1	—	—	—	—	1	2	22
Into brain substance ..	5	—	—	1	—	—	—	—	—	—	—	6
All cases	79	14	16	7	4	1	—	—	1	2	2	126

TABLE 3

MATURITY IN RELATION TO THE TYPE OF HAEMORRHAGE

TYPE OF INTRACRANIAL HAEMORRHAGE	MATURITY			TOTAL
	PREMATURE	FULL-TIME	POSTMATURE	
Subdural (tentorial tears).. ..	9	27	6	42
Subdural (not associated with tentorial tears)	10	7	3	20
Subarachnoid	29	7	—	36
Intraventricular	19	1	2	22
Into brain substance	—	6	—	6
All cases	67	48	11	126

TABLE 4

NATURE OF THE DELIVERY IN RELATION TO THE TYPE OF HAEMORRHAGE

TYPE OF INTRACRANIAL HAEMORRHAGE	DELIVERY						TOTAL
	SPONTANEOUS		INSTRUMENTAL			CAES. SECT.	
	VERTEX	BREECH	VERTEX	*VERTEX PRECEDED BY ROTATION OF HEAD	BREECH		
Subdural (tentorial tears)	11	2	12	14	2	1	42
Subdural (not associated with tentorial tears) ..	6	6	6	2	—	—	20
Subarachnoid	25	5	3	—	—	3	36
Intraventricular ..	16	2	3	—	—	1	22
Into brain substance ..	2	—	4	—	—	—	6
All cases	60	15	28	16	2	5	126

* Manual or instrumental rotation.

TABLE 5

AGE OF MOTHER IN RELATION TO THE TYPE OF HAEMORRHAGE

INFANT	MOTHER'S AGE—YEARS						TOTAL NO. INFANTS
TYPE OF INTRACRANIAL HAEMORRHAGE	UNDER 20	+20–25	+25–30	+30–35	+35–40	OVER 40	
Subdural (tentorial tears)	—	12	11	15	4	—	42
Subdural (not associated with tentorial tears) ..	—	9	9	1	1	—	20
Subarachnoid	—	10	9	13	4	—	36
Intraventricular ..	—	10	5	1	6	—	22
Into brain substance ..	1	—	1	—	2	2	6
All cases	1	41	35	30	17	2	126

TABLE 6

ILLNESS OF THE MOTHER DURING PREGNANCY IN RELATION TO INTRACRANIAL HAEMORRHAGE OF THE NEW-BORN

INFANT		MOTHER															
INTRACRANIAL HAEMORRHAGE		NUMBER SUFFERING DURING PREGNANCY FROM															TOTAL NO. WITH HISTORY OF ILLNESS IN PREGNANCY
TYPE	NO. OF CASES	ECLAMPSIA	PRE-ECLAMPTIC SYMPTOMS	THREATENED ABORTION	ANTE-PARTUM HAEMORRHAGE	HYPEREMESIS	HYDRAMNIOS	SYPHILIS	GONOCOCCAL INFECTION	LEUCORRHOEA	CELLULITIS	FURNUNCULOSIS	PYELITIS	GASTRIC ULCER	ANAEMIA	CARDIAC CONDITION	
Subdural (tentorial tears) .. .. Subdural (not associated with tentorial tears) ..	62	2	4	—	1	2	—	—	1	1	—	—	—	—	—	—	11
Subarachnoid ..	36	—	5	2	—	1	3	—	—	—	—	—	1	1	—	3	16
Intraventricular ..	22	6	7	—	—	—	—	2	1	1	1	1	—	—	1	—	20
Into brain substance ..	6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0
All cases ..	126	8	16	2	1	3	3	2	2	2	1	1	1	1	1	3	47

It is evident that intracranial haemorrhage was contributed to by a variety of factors of which some were ante-natal, others natal and a number post-natal. The interdependence of these factors requires that their relative importance should be judged only in relation to the individual case. In general, however, bleeding into the subarachnoid space and into the ventricular system was associated with prematurity and with illness of the mother during pregnancy ;

and haemorrhage into the brain substance and into the subdural space with instrumental delivery and with delivery at or after term. Intracranial bleeding occurred as a manifestation of a haemorrhagic diathesis in only four cases, all of which were premature, and in two of which it was intraventricular, in one subarachnoid and in a fourth subdural. In cases of intraventricular haemorrhage, illness of the mother during pregnancy was an almost constant finding and was probably a factor of primary etiological importance.

Among cases of subdural haemorrhage, a history of manual or instrumental rotation of the head was a feature of a large proportion of the forceps deliveries (table 4). It was found to be characteristic also of those cases in which subdural bleeding was most extensive at autopsy. The findings suggest that the risks of intracranial haemorrhage associated with instrumental delivery are increased when delivery involves instrumental or manual rotation of the head, a view which has been confirmed in the writer's experience by an analysis of cases surviving intracranial trauma at birth.

The five infants delivered by Caesarian section are of interest in that they included examples of three types of haemorrhage (table 4). In no case was bleeding directly related to the nature of the delivery. Of the three infants with subarachnoid haemorrhage one was premature and the mothers of the remaining two were pre-eclamptics. Subdural haemorrhage occurred in one and intraventricular haemorrhage in the other of two cases in which intraventricular bleeding was a manifestation of a haemorrhagic diathesis. The bleeding in the first-named case came from minute tentorial tears and would probably not have occurred in the absence of a haemorrhagic tendency.

TABLE 7

MORBID CONDITIONS ASSOCIATED WITH DIFFERENT TYPES OF INTRACRANIAL HAEMORRHAGE

TYPE OF INTRACRANIAL HAEMORRHAGE	TOTAL NO. OF INFANTS	NUMBER OF CASES ASSOCIATED WITH						
		PNEUMONIA AND/OR PULMONARY HAEMORRHAGE	HAEMORRHAGE INTO			HAEMATURIA AND/OR PYURIA DURING LIFE; AND/OR RENAL INFARCTION POST MORTEM	EVIDENCES OF A HAEMORRHAGIC DIATHESIS	INFECTION OF SKIN, MUCOUS MEMBRANES OR SUBCUTANEOUS TISSUES
			SUPRARENAL GLAND(S)	INTESTINAL WALL	SEROUS SAC(S)			
Subdural (tentorial tears)	42	17	4	—	—	5	1	9
Subdural (not associated with tentorial tears)	20	6	1	—	—	2	—	6
Subarachnoid ..	36	17	2	3	2	1	2	12
Intraventricular ..	22	13	2	3	3	2	1	8
Into brain substance	6	2	—	—	—	—	—	1
All cases	126	55	9	6	5	10	4	36

TABLE 8

DURATION OF LIFE IN RELATION TO THE TYPE OF HAEMORRHAGE

TYPE OF INTRACRANIAL HAEMORRHAGE	DAY OF DEATH																					TOTAL NO. INFANTS
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Subdural (tentorial tears)	13	9	2	2	2	6	—	—	1	1	—	—	1	—	3	—	—	—	1	—	—	42
Subdural (not associated with tentorial tears) ..	3	1	3	4	5	1	—	—	1	—	2	—	—	—	—	1	—	—	—	—	—	20
Subarachnoid ..	12	6	1	4	5	—	1	—	1	—	—	2	—	—	1	—	1	—	—	—	2	36
Intraventricular ..	5	3	1	1	1	—	3	1	—	—	3	2	—	—	—	—	—	2	—	—	—	22
Into brain substance ..	—	—	—	—	—	1	—	—	—	—	—	1	1	1	—	1	—	1	—	—	—	6
All cases	33	19	7	11	13	8	4	1	3	1	5	5	2	1	4	2	1	3	1	—	2	126

TABLE 9

DURATION OF LIFE IN RELATION TO THE TYPE OF HAEMORRHAGE AFTER ELIMINATION OF CASES WITH PULMONARY INFLAMMATION OR HAEMORRHAGE

TYPE OF INTRACRANIAL HAEMORRHAGE	DAY OF DEATH																					INFANTS	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	NO. WITH PULMONARY COMPLICATIONS	TOTAL
Subdural (tentorial tears)	8	6	2	1	2	3	—	—	1	—	—	—	1	—	1	—	—	—	—	—	—	17	42
Subdural (not associated with tentorial tears) ..	3	1	2	4	3	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6	20
Subarachnoid ..	10	4	1	3	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	17	36
Intraventricular ..	4	1	1	—	1	—	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	13	22
Into brain substance ..	—	—	—	—	—	1	—	—	—	—	—	1	1	—	—	—	—	1	—	—	—	2	6
All cases ..	25	12	6	8	7	5	—	1	1	—	—	2	2	—	1	—	—	1	—	—	—	55	126

The six infants with haemorrhage into the brain substance were noteworthy fort he similarity of the clinical pictures they presented (p. 104) and for distinctive features common to their antenatal and natal histories. Delivery at term of a large, first child by a mother at the extremes of the reproductive period was a feature of the birth of five of the infants (tables 4 and 5). The remaining infant was a fourth child given birth to by a mother aged twenty-nine who on admission to hospital showed evidence of uterine inertia. In the absence of evidence of a contracted pelvis, and of a history of illness during pregnancy in connexion with all six mothers, haemorrhage in these cases would appear to have resulted from an unusual combination of factors making for prolonged and difficult labour.

The cases are too few in number to allow of definite conclusions being arrived at, but they are of especial interest in that they represent a clinical entity.

Equal importance attaches to the group consisting of three infants in whom there was pathological evidence of recurrence following earlier arrest of intracranial bleeding. Death of one infant took place on the sixth, of another on the ninth and of the third on the fifteenth day of life. In each case death was sudden and followed a period during which clinical evidence of post-natal intracranial haemorrhage had gradually disappeared. One infant was removed from hospital contrary to advice only to return within the space of a few hours, having in the interval gone into coma following a succession of violent convulsions. The second infant threw fits after having been lifted from its cot without permission. The remaining infant suffered a relapse on the eighth day within a few minutes of fixing at the breast for the first time. Initial attempts at suckling were followed by twitching movements of the extremities which rapidly developed into convulsions and culminated in death within six hours. These three cases illustrate the risks already referred to (p. 95) of ill-considered handling during convalescence from intracranial haemorrhage. For these risks to be avoided it is necessary that nursing management should be subject to strict medical supervision and that all movements of patients should be reduced to a minimum. Cases of intracranial haemorrhage in the present series include a number of infants sent to hospital on account of their critical condition following delivery at home. In several instances removal to hospital had involved a road journey of ten miles or more. It is doubtful if the worst of home conditions justified such removal or if the best of hospital provisions could compensate for the risks of transport. The need in such cases is for domiciliary treatment and is one which, should the necessity arise, can be met by utilizing available public health services.

Diagnosis

Appropriateness of treatment is largely dependent upon the accuracy of diagnosis. Diagnosis in the new-born infant is associated with difficulties peculiar to the age of the patient, and in no condition are these difficulties more in evidence than in intracranial haemorrhage. A moribund state associated with gross asphyxia and rapidly terminating in death, or prematurity associated throughout life with extreme frailty were features of the picture presented by those infants of the series who showed no clinical signs distinctive of intracranial bleeding. Of cases in which a diagnosis of intracranial haemorrhage was not made during life the bleeding was subarachnoid in twenty-two, subdural in twenty and intraventricular in six. Of fourteen cases in which only a tentative diagnosis was made haemorrhage was subarachnoid in four and subdural in ten. A diagnosis was made during life in the case of all the infants with haemorrhage into the brain substance. The observations made in connexion with each type of case indicate that while certain clinical features were associated with all forms of intracranial haemorrhage, others were characterized by their occurrence in association with only one or more particular types. Recognition of

the fact allowed of a differential diagnosis being made in an appreciable proportion of cases.

In many instances the clinical picture presented by the infants was in itself sufficient to suggest a diagnosis of intracranial haemorrhage. Consideration of the mother's ante-natal history and of the details of the labour was essential for diagnosis in some cases, and in others allowed of a diagnosis being made at an earlier stage than would have been possible had reliance been placed solely on clinical findings. Account was taken of the preponderance of first children and of premature infants, the risks associated with forceps delivery and particularly when such delivery followed instrumental or manual rotation of the head, the factors which may combine to make delivery of a mother at the extremes of the reproductive period of a first child difficult, the frequent association of illness of the mother during pregnancy and haemorrhage in the infant, and the possible existence of intracranial haemorrhage in cases showing evidences of a tendency to bleed.

Considerable importance was attached to severe or prolonged asphyxia as evidence of existing haemorrhage or of possible future bleeding. Improvement during the first thirty-six hours of life in a child suspected of suffering from intracranial haemorrhage was only rarely found to warrant revision of the original diagnosis, confirmation of which was usually forthcoming in the gradual appearance of symptoms of cerebral pressure and motor irritation. Characteristic clinical signs included a persistent disinclination for fluids, agitated movements of the eyes, inequality of the pupils and an anxious expression which suggested that the restlessness which later accompanied it was one of mind more than of body. The facial expression was in itself distinctive, was characteristic of a great majority of cases and had a particular value in that it was recognizable at an early stage. Darting protrusion of the tongue was an inconstant but characteristic sign of intracranial haemorrhage. It was not seen in any one of 200 control infants suffering from other diseases of the new-born. Convulsive twitching movements of the extremities occurred frequently in other neonatal conditions and were considered to be indicative of an intracranial condition only in the presence of other suggestive signs and symptoms. The significance of convulsions in cases of cerebral haemorrhage was frequently confirmed by a cerebral cry or by changes in the tension of the fontanelle in infants at rest. Bulging of the fontanelle served to confirm the diagnosis in a limited number of cases, but fullness or ' sponginess ' as distinct from bulging was of greater value as an early indication of haemorrhage. Taken in conjunction with other symptoms, vomiting when only occasional and when not attributable to swallowed mucus was of some significance. General failure to progress, variability in reflex responses and spastic flexion of the limbs and extremities were among other features which when present completed the clinical picture. In no case was the clinical picture typical of tetany.

Subdural haemorrhage was the most common type of intracranial bleeding. It was associated more frequently with maturity than prematurity, and with instrumental than spontaneous delivery ; and was the type of haemorrhage found in the majority of postmature infants. Some degree of asphyxia at

birth followed by a period of limited improvement in the general condition was characteristic of cases surviving more than a few hours. An unnatural alertness and anxiety of expression was the earliest, most constant and most reliable clinical sign. It resembled the facies of intraventricular and of intracerebral haemorrhage in the mental restlessness it betrayed, but lacked the impression of agonized suffering in the face of the infant with bleeding into the ventricles, and of fear in the expression of infants with intracerebral bleeding. Customarily the anxious expression was apparent within thirty-six to forty-eight hours of birth and served to distinguish cases of subdural haemorrhage from those in which the condition was one of intense asphyxial congestion. It was characteristic alike of depressed and irritative clinical phases. In general the symptoms of subdural haemorrhage were more conspicuous than those of subarachnoid or intracerebral haemorrhage. Convulsive movements of the limbs, incoordinated movements of the eyes and reflex irritability were more pronounced and, generalized increase of muscle tone was more common and more sustained. Subdural haemorrhage below the tentorium resembled intraventricular bleeding in giving rise in some cases to nuchal rigidity and to some degree of head retraction, but differed in that it was associated with a cyanosis, which was typically deep and persistent. In a limited number of cases it was associated with athetoid movements and tremors of the extremities not seen in any other form of intracranial haemorrhage.

Subarachnoid haemorrhage was the most difficult form of intracranial bleeding to recognize. Clinical signs were absent or indefinite more frequently in cases of subarachnoid haemorrhage than in other types of intracranial bleeding. In some cases diagnosis was one largely of elimination and presumption based upon the presence of such predisposing factors as prematurity and antenatal debility of the mother, and upon the absence of signs suggestive of other types of cerebral haemorrhage. Subarachnoid haemorrhage resembled intraventricular haemorrhage in that the first appearance of symptoms was sometimes delayed until after the first week of life and always followed a period during which weight had failed to progress. It differed from intraventricular haemorrhage in that the onset of symptoms was gradual and that severe symptoms were absent. It was associated with frailty which was consistent with the prematurity of the majority of the cases and which was readily distinguishable from the combination of physical weakness and exhaustion characteristic of cases of intracerebral haemorrhage. Of the different types of intracranial bleeding, subarachnoid haemorrhage was the only one in which a study of the facies was of little diagnostic value. Slight twitching of the extremities and rapid, incoordinated movements of the eyes were findings which when they occurred in a frail, premature infant showing no signs of progress, were of some value in suggesting the possible presence of subarachnoid haemorrhage.

Intraventricular haemorrhage differed from other forms of intracranial bleeding in the absence of an initial stage of depression, the dramatic suddenness of its onset, the severity of the symptoms to which it gave rise, and the rapidity with which death followed on the first appearance of symptoms. It was the form of haemorrhage most frequently found in infants in whom evidence of

intracranial disturbance did not appear until after the first week, and resembled infratentorial haemorrhage into the subdural space in mature infants in occasionally giving rise to nuchal rigidity and head retraction. It occurred only in premature infants, invariably followed a period during which the weight had remained stationary, and was remarkable for an almost constant association with illness of the mother during pregnancy. Symptoms were characterized by a severity which was the more striking occurring as they did in premature infants. Bulging of the fontanelle was appreciable to the naked eye. The cry and expression betrayed agonizing pain in a manner not typical of any other intracranial condition. Painful crises were suggested by a characteristic occurrence of periods of great violence followed by complete physical exhaustion. Lumbar puncture afforded considerable but only temporary relief and invariably resulted in undiluted blood being obtained under great pressure. A terminal rise of temperature was typical. Meningitis may simulate intraventricular haemorrhage, but, as indicated elsewhere (Craig, 1936), is characterized by a purulent cerebro-spinal fluid, a less abrupt onset, symptoms of less severity and by pyrexia for some days prior to death.

Haemorrhage into the brain substance occurred only in large children delivered at term after a prolonged labour. It was characterized by a vague indefinite onset, a prolonged course and a slow death, a progressive, uninterrupted and at times precipitous decline in weight from the day of birth, a low body temperature and an abnormally, flaccid inactivity, and by extreme physical weakness. The facies were typical. Sullen and frowning at first, the expression became one of fear as distinct from that of pain described in connexion with intraventricular haemorrhage. The association of continuous mental restlessness with extreme physical weakness distinguished these cases from all other forms of intracranial haemorrhage. The absence of other findings commonly met with in cases of cerebral haemorrhage was an important point of diagnosis. Difficulty in diagnosis arose from the essential insidiousness of these cases. The difficulty was one of diagnosis as distinct from differential diagnosis. A diagnosis of intracranial bleeding in these cases implied recognition of the type of haemorrhage.

Associated conditions

The difficulties of diagnosis were sometimes added to by the association of intracranial haemorrhage with other morbid conditions. Pathological processes were present elsewhere than within the cranium in a large number of cases and occurred in association with intracranial haemorrhage of all types (table 7). Pulmonary lesions predominated. They were detected during life in the majority of cases, but differentiation of pneumonia from intrapulmonary haemorrhage was not possible. Improvement in colour following the administration of oxygen has been described (Craig, 1935*a*) as characteristic of pulmonary consolidation in the new-born. It proved of value in the present series as an indication of complicating pneumonia or intrapulmonary haemorrhage. In cases of cerebral haemorrhage in which the lungs were healthy or

only atelectatic the degree of cyanosis was not influenced by oxygen therapy. In a number of cases the pulmonary lesions were sufficiently extensive to have accounted for death had other pathological conditions not been present. In a few cases, consisting mainly of those with subarachnoid haemorrhage, it could be said with some confidence that as a contributory cause of death the pulmonary lesion had been of greater importance than the cerebral condition. In others it was apparent that pneumonia was a terminal event, but in a considerable number it was impossible to judge of the relative importance of intracranial haemorrhage and pulmonary consolidation as the primary cause of death.

A comparison of tables 8 and 9 is of interest in this connexion. It shows that pulmonary lesions were present at death in twenty-three (74 per cent.) of thirty-one infants surviving the first week of life and in thirty-two (33 per cent.) of ninety-five infants dying within seven days of birth, and that of uncomplicated cases of cerebral haemorrhage the great majority died during the first week of life. The figures are sufficiently striking to suggest that of infants in the series a number would have survived had pulmonary complications not supervened.

Pulmonary lesions were found in association with all types of intracranial haemorrhage. Intraventricular haemorrhage differed from other forms of intracranial bleeding in that the interval separating the onset of symptoms and death never exceeded and was frequently less than two days. It is probable that the massive haemorrhage present in the lungs of some of these cases occurred simultaneously with that into the ventricles. In contrast, pneumonia in cases of intraventricular bleeding almost certainly preceded the onset of haemorrhage of which it must be regarded as having been a potentially, predisposing factor. It is not improbable that pneumonia may be of equal importance in the etiology of other forms of intracranial haemorrhage and that it is incorrect to assume that in them it occurs only as a late sequela. Similar significance may attach to other forms of infection noted in connexion with a number of infants included in the investigation (table 7).

The abnormal findings in the kidneys of ten infants with cerebral haemorrhage (table 7) are of interest in this connexion. Discussing urinary disorders in the neonatal period Craig (1935*b*) described one infant in whom pyelitis preceded fatal intraventricular haemorrhage, and nine infants in whom urinary infection occurred as a late complication of intracranial haemorrhage, of whom one died and was found at autopsy to have an extensive tentorial tear and a massive subdural haematoma. The two fatal cases are included in the present series. The incidence of urinary infection in cases of cerebral haemorrhage is sufficient to merit attention, but does not warrant dogmatic conclusions. The fact that haemorrhage was intraventricular in the one case in which symptoms referable to it were preceded by urinary infection is at least of interest in view of the frequent association of intraventricular haemorrhage with pneumonia. It is possible that in this case urinary infection favoured intraventricular haemorrhage in a way similar to that postulated in connexion with pulmonary infection. In the other cases the late occurrence of urinary complications may be attributed

to an aggravation of physiological factors. Passive hyperaemia of the kidneys, limited excretion and a concentrated urine are normal features favouring infection of the urinary tract during the early days of life. In cases of cerebral haemorrhage, asphyxia and an impaired circulation intensify renal congestion, concentration of the urine is increased as a result of a limited fluid intake, flushing of the kidney tubules and pelvis is reduced to a minimum and favourable conditions are created for bacterial growth and multiplication. There is evidence in support of the theory in the frequency with which a negligible urinary output was noted in connexion with cases of the present series. Uncomplicated neonatal pyelitis is not a dangerous condition when promptly treated and recovery of the cases already referred to suggests that it is only rarely fatal when a sequela of cerebral haemorrhage. Nevertheless, the condition is one of sufficient severity to require that every endeavour should be made to prevent its occurrence in infants recovering from intracranial conditions. The clinical problem presented is a difficult one and consists in determining the maximum amount of fluid which can be given consistent with the requirements of the cerebral condition.

The management of cases of intracranial haemorrhage must take account of the dangers and possible consequences of complications. It requires the most skilled of nursing attention. I hold no brief for the view sometimes expressed that recovery is not always desirable. From a follow-up from birth of a large number of recovered cases I am satisfied that the severity of symptoms during the early days of life does not afford a reliable indication either as to the possibility or otherwise of subsequent physical or mental impairment, or of the probable extent of such disability should it eventually develop. It is due to every new-born infant, the victim of cerebral haemorrhage or in virtue of predisposing factors in danger of cerebral haemorrhage, that he should receive skilled nursing comparable with that ordinarily available to an adult case of pneumonia or typhoid. In order that skilled treatment may be more readily and more universally available it is desirable that increasing attention be paid in the training of medical students and of pupil midwives to the care and treatment of the new-born infant in health and disease.

Greater familiarity of those responsible for the care of new-born infants with conditions as they are found in the early days of life would minimize the risks of intracranial haemorrhage attendant upon post-natal factors. It would in all probability contribute to a reduction in the neonatal mortality rate which represents one of the outstanding problems requiring investigation.

Summary

1. A series of 126 infants in whom intracranial haemorrhage was found post mortem is described. Clinical observations made from the time of birth and the pathological findings at autopsy are given.

2. The cases are grouped and clinical and pathological observations in connexion with them recorded, according to the distribution of the intracranial bleeding. Subdural haemorrhage was present in sixty-two, subarachnoid

haemorrhage in thirty-six, intraventricular haemorrhage in twenty-two, and haemorrhage into the brain substance in six infants.

3. In general subdural haemorrhage was associated with tearing of the tentorium, maturity and instrumental delivery ; subarachnoid and intraventricular haemorrhage with prematurity and with illness of the mother during pregnancy ; and haemorrhage into the brain substance with prolonged labour and with delivery of a mother at the extremes of the reproductive period of a large first-born child. Intracranial haemorrhage occurred as a manifestation of a haemorrhagic diathesis in only four cases.

4. It is suggested that toxaemia or infection (or both) of the mother during pregnancy is a factor of primary etiological importance in cases of intraventricular haemorrhage ; and that the risks of cerebral haemorrhage associated with forceps delivery are increased when delivery is preceded by manual or instrumental rotation of the head.

5. Diagnosis is discussed and the value of physiognomical diagnosis emphasized. Importance is attached to an anxious expression ; to restlessness of mind rather than of body ; and to ' sponginess ' rather than tension or bulging of the fontanelle as early and reliable diagnostic signs. It is considered that although not always present, ' adder-like ' protrusion of the tongue occurs only in cases of intracranial haemorrhage.

6. The clinical pictures associated with the different types of intracranial haemorrhage are compared. Attention is drawn to the indefiniteness and frequent absence of clinical signs in cases of subarachnoid haemorrhage ; to the successive periods of improvement, irritation and depression in cases of subdural haemorrhage ; to the sudden onset, violent symptoms, short course and terminal hyperpyrexia in cases of intraventricular haemorrhage ; and to the prolonged course, the uninterrupted, progressive fall in weight, the association of mental restlessness with extreme physical weakness, the low body temperature and the insidious decline characteristic of infants with haemorrhage into the brain substance.

7. The frequency with which intracranial bleeding is associated with other pathological conditions is emphasized. Pneumonia, intrapulmonary haemorrhage and superficial infections together or separately are described as common and urinary infection as occasional complications. It is considered that in some cases infection is related to the etiology of intracranial haemorrhage ; and that the scanty urinary output associated with cerebral haemorrhage favours infection of the urine.

8. The view is held that among infants showing symptoms of cerebral haemorrhage death of a number is attributable to the development of complications. The dangers of ill-considered handling ; the risks of removal to hospital and the desirability of domiciliary treatment of infants born at home and showing symptoms of intracranial trauma ; and the necessity for skilled nursing are emphasized.

9. A plea is submitted for the improved instruction of medical students and pupil midwives in the health and diseases of the new-born infant as necessary for a reduction in the neonatal mortality rate.

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VITAMIN C EXCRETION IN CHILDREN, WITH PARTICULAR REFERENCE TO RHEUMATIC FEVER

BY

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In the study of vitamin C deficiencies a large volume of work has accumulated in the literature. A considerable amount of the work based on biochemical estimations is conflicting owing to sources of error in method and to other interfering factors. The interpretation of the results obtained and their application to clinical data thus becomes difficult in many instances. The purpose of this investigation was to study the excretion of vitamin C in normal children and in children suffering from various diseases, with particular reference to rheumatic fever, and at the same time to investigate the limitations in interpreting results obtained by biochemical estimation of the vitamin in urine.

Previous investigations

Harris and Ray (1935) found the normal adult excreted 15–30 mgm. of ascorbic acid in the urine in twenty-four hours on a normal diet. Since then, other investigators have found similar figures, and Hawley and others (1936) give 15–28 mgm. as the normal daily excretion in an adult. In children, Hess and Benjamin (1934) reported that appreciable amounts of vitamin C could be detected in the urine only when large amounts were present in the diet. They concluded that the amounts of the vitamin in the urine of children under normal dietary conditions is negligible and when present in significant amounts represents an excess which appears after complete saturation of the tissues. Rohmer and others (1934) found measurable amounts in the urine of infants. When they were put on a diet low in vitamin C they continued to excrete it in the urine. From this it was concluded that they could synthesize vitamin C in the body. In older children, it was found that the output fell to unappreciable levels when a deficient diet was used.

Harris and Ray (1935), studying scorbutic infants, found low amounts in the urine, viz. 0·4–0·7 mgm. per day. After treatment, when they became

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saturated, excretion varied from 1·4 to 2·4 mgm. (two cases). In control infants the daily excretion was 1–3 mgm. They suggest that children excrete the same amount of the vitamin as adults when expressed in terms of body weight.

Most of the experimental work relating to infection and vitamin C has been on animals. Harde and Phillippe (1934) showed that the adrenal cortex of animals dying from diphtheria toxins had reduced vitamin C content. Furthermore, when 2 M.L.D. of diphtheria toxin was in contact with 10–20 mgm. of ascorbic acid for one hour it lost some of its toxic properties. The classical symptoms of diphtheria were not produced in guinea-pigs inoculated with this amount of altered toxin, whereas controls could not withstand the effect of 2 M.L.D. They found the ascorbic acid content of the adrenals and livers of laboratory animals was reduced in many other infections and intoxications. Harde and Rothstein (1935) estimated the vitamin C excretion in ten cases of pneumonia and found the output was slightly less than normal. Saturation tests revealed a greater degree of unsaturation than normal.

From experimental work on animals, Rhinehart and Mettier (1934) presented evidence that rheumatic fever is due to a vitamin C deficiency associated with infection. Guinea-pigs rendered scorbutic and sub-scorbutic by vitamin C-deficient diets were infected with a streptococcus. They developed lesions on the heart valves regarded as similar to those of acute rheumatic fever. A mosaic arrangement of cells at the junction of the heart valves was found on histological section, but no typical Aschoff bodies could be seen. Other workers have produced similar lesions in guinea-pigs, but no one has succeeded in producing typical Aschoff bodies as found in acute rheumatic fever.

Perry (1935) studied the excretion of vitamin C in the urine following a single test dose of 500 mgm. He used five acute cases of rheumatic fever and six quiescent cases. Three in each group showed no apparent deficiency. The others were soon brought to a state of saturation by repeated doses. He concluded that vitamin C deficiency was not an important factor in the production of acute rheumatic fever. Sendroy and Schultz (1936) in a recent investigation examined thirty-three patients from this point of view. Thirteen were suffering from acute rheumatic fever, thirteen were inactive convalescent cases of rheumatism and seven were controls. They were all given 250 mgm. of ascorbic acid daily for seven days and the vitamin C excreted in the urine was estimated quantitatively over that period. Eight of the acute rheumatic cases showed some deficiency, but of these eight, two had previously had a poor diet and six had been vomiting, which, it was concluded, accounted for most of the deficiency. In any case the deficiency was slight when the output of the controls was considered. It was concluded there was no support for the concept that a condition of ascorbic acid deficiency is a predisposing factor in rheumatic fever. These authors also fed large doses of ascorbic acid over a period of several months to a group of cases of rheumatism. The clinical manifestations of the disease were not demonstrably affected.

A contrary view is taken by Abbasy, Hill and Harris (1936), who found a striking difference between the range of values for the excretion of vitamin C in the urine of rheumatic patients (active and convalescent) and those of control subjects. The average daily output was less in the rheumatism group than in the controls, but was almost identical with that of a group of children with active tuberculosis. They recommend the use of orange juice therapeutically and prophylactically in rheumatic fever, and suggest that the low value of vitamin C in the urine might be used in conjunction with clinical evidence as a diagnostic index of juvenile rheumatism for revealing the presence of a continued latent infective process.

Present investigation

The vitamin C in the urine was estimated quantitatively by the method of Harris (1935). Urines were examined immediately they were obtained during the day. The night urine was collected in a bottle containing 50 c.c. of acetic acid and examined as early as possible in the morning. In this way the minimum alterations in vitamin C due to standing were obtained. Specimens were collected for three days and the average for twenty-four hours determined.

Diet.—The diet provided was the usual hospital diet and supplied a daily intake of approximately 40 mgm. of ascorbic acid for children between four and thirteen years with whom this study is mainly concerned. It would have been more satisfactory to place each child investigated on a diet free from vitamin C and to administer ascorbic acid in weighed quantities. However, since so many children suffering from a variety of diseases in various parts of the hospital were studied, this was decided to be impracticable. If this test was to prove useful in the routine study of cases the simplest possible régime seemed desirable. The vitamin C in the diet was kept as constant as possible during the period of investigation. Using relatively large groups of patients it was considered possible to draw conclusions from the results obtained in this way after estimating the daily excretion of vitamin C.

Wide variation in the amount of vitamin C excreted was found in children of the same age and on the same diet. As a rule, however, older children excreted more than the younger ones. The average excretion in twenty-four hours for a group of thirty-nine children who had little or no evidence of infection in the medical and surgical wards of the hospital was 9·7 mgm. Their ages were from two to thirteen years. When this group was divided in two according to ages, it was found the average for those between two and six years was 5·5 mgm. and 11·5 mgm. for those between seven and thirteen years. This indicates a definite increase in output with age, but when the variations in each group are considered the relationship appears less definite. Those in the first group (two to six years) varied in their excretion in twenty-four hours from 3·9 mgm. to 25·0 mgm. and in the second group (seven to thirteen years) from 4·5 to 35·6 mgm. The main point in these observations is that the total daily excretion of vitamin C provides inadequate information to determine the presence or absence of a deficiency. A similar variation in results was noted when test doses were used.

A daily test dose of 500 mgm. of ascorbic acid has been used by several investigators to determine the degree of saturation of a patient. This amount was used in this study and administered daily while quantitative changes of the vitamin in the urine were measured. A diversity in response was found in different patients. Thus, in one patient the amount of the vitamin excreted rapidly rose to 200 mgm. per day and then continued at this level, while in another a much higher amount was reached. One child excreted 480 mgm. (96 per cent. of the test dose) before assuming a constant output at this level. Similar results were obtained by Hawley and co-workers, who found a marked

variation in twelve adults in response to test doses. They suggest that factors, hitherto unknown in the urine, may interfere at times and in certain individuals with the accurate measurement of the vitamin.

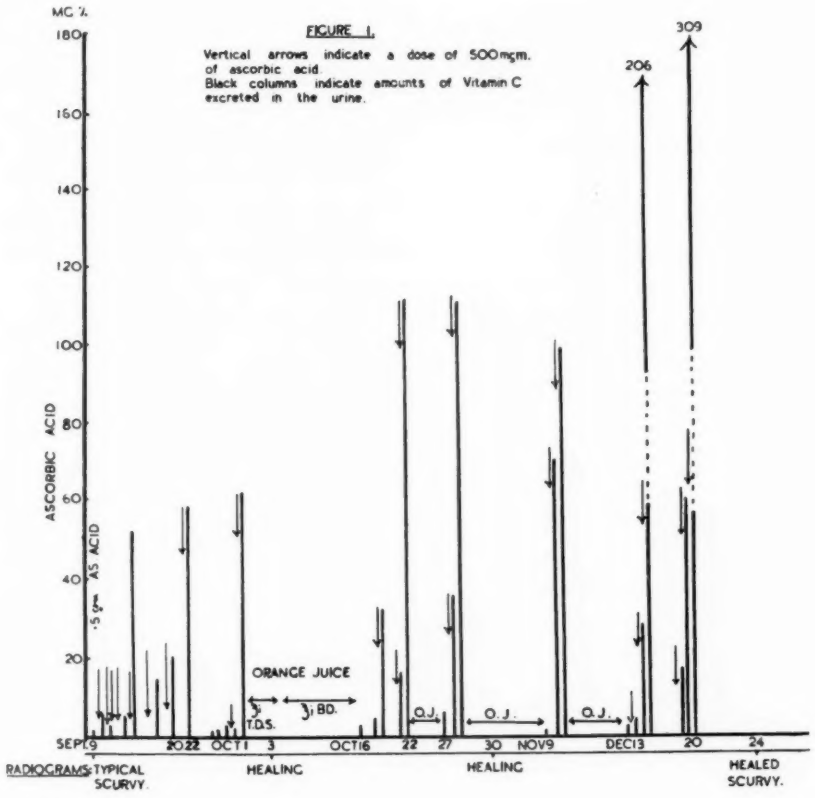
It was found difficult to ascertain the point where saturation was reached. A normal child may excrete nearly 50 mgm. of vitamin C after one test dose of 500 mgm. About two-thirds of the normal cases in this series were found to excrete slightly more than this after the first test dose. After daily administration of 500 mgm. vitamin C it required several days to reach a maximum excretion. It appeared most probable that this maximum occurred when an abnormal degree of saturation was reached. Because this maximum varied widely from one child to another, it was not considered a suitable basis for comparison, and for the purposes of this investigation a child has been considered saturated when after a test dose of 500 mgm. of ascorbic acid he excreted 50 mgm. in his urine in the following twenty-four hours.

The response to test doses is best studied in a vitamin C-deficient state such as scurvy. At this hospital during the past two years, nine children suffering from scurvy have been investigated in this way, and it is interesting to note that these infants required almost as much ascorbic acid to saturate them as an adult with the same disease. They required from 1·5 gm. to 3·25 gm. of ascorbic acid, whilst an adult with scurvy, reported by Archer and Graham (1936), required from 2 to 3 gm. to produce a similar state of saturation.

Infants with scurvy, in spite of severe manifestations of the disease, continue to excrete small amounts of the vitamin in the urine. Sometimes after therapeutic doses of vitamin C are given, the amount in the urine falls still further and remains low until a state of saturation is approached. Variations in the output of vitamin C after administration of pure ascorbic acid to an infant suffering from scurvy and during the healing process are shown in the following case :

L.D., aged eight months, was admitted to hospital on September 9, 1936, with pain and swelling in the legs of one month's duration. He had been fed on cow's milk, water and sugar from birth, and had never received any orange juice. The skiagrams of arms and legs showed the typical changes of scurvy. He was not given orange juice at first, but ascorbic acid was administered in doses of 500 mgm. These doses are indicated in fig. 1, which also shows the output of ascorbic acid in the urine during the period of observation. Orange juice was started, one teaspoonful thrice daily, on October 3, 1936, and increased to one oz. twice a day on October 8. This was stopped subsequently whenever tests were done for vitamin C in the urine. Skiagrams of the bones were taken on several occasions to indicate the progression of the reparative process. The consecutive evidences of clinical and pathological improvement may be set down as follows, and it is interesting to note that they do not coincide with one another in time. (1) The symptoms of pain and irritability disappeared completely within the first two days after the start of treatment. (2) Judging by the arbitrary standard described above, saturation occurred six days after admission, i.e. his excretion of vitamin C showed a sudden rise to over 50 mgm. after five successive doses of 500 mgm. of ascorbic acid. However, when a few days were allowed to lapse with no treatment, the response to another test dose was again very low, and several doses had to be given to bring the excretion

up once more to over 50 mgm. (3) It was not until November 10 that, following one dose of 500 mgm. of ascorbic acid, the output was immediately over 50 mgm., and several doses were not necessary to produce this amount. (4) Healing was not complete in the skiagrams until December 12, viz. fourteen weeks after the beginning of treatment.



This serves to illustrate some of the difficulties in interpreting saturation tests in relation to scorbutic or sub-scorbutic patients. While it does not take many doses of ascorbic acid to produce a sudden and marked rise in the excretion of vitamin C (five consecutive doses of 500 mgm.) in a child with acute scurvy, it is many weeks before the patient is completely cured. Biochemically it is not easy to differentiate between the various stages of the disease. For this reason recognition of sub-scurvy by this means has been regarded as indefinite and interpretation of results made with reserve.

Results

Table 1 shows the output of ascorbic acid by children in a control group in this hospital. Sixty-nine children who had been admitted to the medical and surgical wards with little or no evidence of active infection were chosen for this group. They had been admitted for hernial repair, removal of naevi, epilepsy, mild or questionable bronchiectasis, and were investigated shortly after admission to hospital and while on the ordinary hospital diet. The average daily output of vitamin C in the urine was found to be 9·7 mgm. Eighteen of these patients were then given daily test doses of 500 mgm. of ascorbic acid and the amount appearing in the urine was estimated : 61 per cent. excreted 50 mgm. or more following the first dose. The rest required two or three doses to produce this response in the urine, but none required more than three.

TABLE 1

OUTPUT OF ASCORBIC ACID BY 39 MEDICAL AND SURGICAL PATIENTS WITH LITTLE OR NO EVIDENCE OF INFECTION

Average daily excretion of ascorbic acid during control period = 9·7 mgm.
Range = 3·9 — 35·6 mgm.

Divided into Age Groups.

A. 2–6 years : average daily output = 5·5 mgm. ascorbic acid.
Range = 3·9–25 mgm.

B. 7–13 years : average daily output = 11·5 mgm. ascorbic acid.
Range = 4·5–35·6 mgm.

18 children were then given daily test doses of 500 mgm. of ascorbic acid by mouth.

11 out of 18 required 1 dose before 24 hours' output reached 50 mgm.	.. 61 per cent.
2 out of 18 required 2 doses before 24 hours' output reached 50 mgm.	.. 11 per cent.
5 out of 18 required 3 doses before 24 hours' output reached 50 mgm.	.. 28 per cent.

Table 2 shows the results obtained by tests carried out on eighteen patients at the convalescent home associated with the hospital. These children were recovering from empyema, asthma, chronic bronchitis, nephritis, and severe upper respiratory tract infection. The diet was similar to that given to the children referred to in table 1. The average daily output was 9·3 mgm. Fifteen of these children were then given daily test doses of 500 mgm. of ascorbic acid. Seven, or 46 per cent. required one dose to produce a response of 50 mgm. or more in the urine in the twenty-four hours following. All were ' saturated ' by the third dose. Although the average daily output during the control period was the same as for those in table 1, the response to test doses of vitamin C was less satisfactory, and it would appear that these children did not have the same stores of the vitamin and were therefore unsaturated in comparison.

TABLE 2

OUTPUT OF ASCORBIC ACID BY CONVALESCENT PATIENTS RECOVERING FROM VARIOUS DISEASES SUCH AS EMPYEMA, ASTHMA, BRONCHIECTASIS, GENERAL DEBILITY

Average diet of the convalescent home.
Average daily output during control period of 18 cases was 9·3 mgm.

15 were then given a daily dose of 500 mgm. ascorbic acid.

7 required 1 dose before 24 hours' output reached 50 mgm.	46 per cent.
6 required 2 doses before 24 hours' output reached 50 mgm.	40 per cent.
2 required 3 doses before 24 hours' output reached 50 mgm.	14 per cent.

Table 3 records the results on six patients who were suffering from severe infection such as acute pneumonia, advanced tuberculosis and advanced Hodgkin's disease. The average daily output was 8·4 mgm. and only one was saturated after the first dose of ascorbic acid.

TABLE 3

OUTPUT OF ASCORBIC ACID BY 12 PATIENTS WHO WERE SUFFERING FROM INFECTIONS AND WHO WERE ON AVERAGE HOSPITAL DIET

Average 24 hours' output of ascorbic acid in the urine = 8·4 mgm.

6 were then given 500 mgm. of ascorbic acid daily.

1 required 1 dose of ascorbic acid before 24 hours' output reached 50 mgm.
2 required 2 doses of ascorbic acid before 24 hours' output reached 50 mgm.
3 required 3 doses of ascorbic acid before 24 hours' output reached 50 mgm.

Tables 4 and 5 deal with the rheumatic fever patients studied. In table 4 are recorded the results in acutely-ill cases at the time of admission to hospital. The vitamin C in the diet was about the same as that of the children in the other groups. The average daily output was 21·5 mgm. This is almost double the figure for the controls ; the factors influencing this will be discussed later : 50 per cent. were saturated after the first dose, and none required more than three doses to produce a response of 50 mgm. ascorbic acid in the urine. This indicates a mild degree of unsaturation of stores as compared with the controls.

TABLE 4

PATIENTS WITH ACUTE RHEUMATIC FEVER ON AVERAGE HOSPITAL DIET AS TOLERATED AT THE TIME OF ADMISSION

Average daily output during 24 hours' control for 18 cases = 21·5 mgm.

These 18 cases were then given 500 mgm. ascorbic acid daily.

9 required 1 dose before 24 hours' output reached 50 mgm.	50 per cent.
7 required 2 doses before 24 hours' output reached 50 mgm.	39 per cent.
2 required 3 doses before 24 hours' output reached 50 mgm.	11 per cent.

TABLE 5

CONVALESCENT RHEUMATIC PATIENTS ON CONVALESCENT HOME AVERAGE DIET

Average daily output during 24 hours. control period for 31 cases = 12·4 mgm.

18 were then given 500 mgm. ascorbic acid daily.

11 out of 18 required 1 dose before 24 hours' output reached 50 mgm.	.. 61 per cent.
3 out of 18 required 2 doses before 24 hours' output reached 50 mgm.	.. 17 per cent.
3 out of 18 required 3 doses before 24 hours' output reached 50 mgm.	.. 17 per cent.
1 out of 18 required 4 doses before 24 hours' output reached 50 mgm.	.. 5 per cent.

Table 5 deals with fifty-one convalescent rheumatic patients. The average daily output was 12·4 mgm., whilst children convalescing from other diseases in the same institution averaged 9·3 mgm. per day. Eighteen were given daily test doses and 61 per cent. of these were found to be ' saturated ' after the first dose. One child required four consecutive doses to put his excretion up to 50 mgm. a day in spite of the fact that he had been receiving an adequate diet of vitamin C for several months. He was not ill and showed no other signs of deficiency of this vitamin. It seems likely that certain unknown interfering factors were present which produced this unusual result.

Since many of the acute cases of rheumatic fever were receiving salicylates and bicarbonate, it was decided to give similar doses of these drugs to a group of the controls and study the effect on the excretion of vitamin C. Fifteen of the children in the control series (table 1) were used for this purpose. The average daily output of those chosen was found to be 12·2 mgm. Then 50 grains of sodium salicylate and 100 grains of sodium bicarbonate were administered each day for three days. During this treatment the average daily excretion of ascorbic acid rose to 15·9 mgm. These results are recorded in table 6, and may explain in part the higher average excretion of ascorbic acid in the acute stages of the disease, since about one half of those included in table 4 were receiving similar doses of sodium salicylate and sodium bicarbonate. The figures in table 4 have been analysed with this in mind and some increased excretion was noted in the group receiving salicylates. Of the eighteen patients with acute rheumatic fever seven were receiving sodium salicylate and bicarbonate and had an average daily excretion of 24 mgm. ascorbic acid ; while the eleven who were receiving no medication had an average daily excretion of 20 mgm. ascorbic acid. Some of those not receiving salicylates excreted abnormally large amounts of vitamin C daily. On the other hand these findings may possibly be explained on the basis of some recent work by Payne (1936), who showed that there is an increase in the total acidity and various acid constituents of the urine in acute rheumatic fever. Hawley, Daggs and Stephens (1937) have shown that an increase in the acidity of the urine increased the excretion of ascorbic acid and a diminution in the acidity of the urine resulted in a decrease of the vitamin C content of the urine, and it seems quite possible that this may be a factor of importance in acute rheumatic fever in producing an abnormally high excretion of vitamin C.

TABLE 6

THE EFFECT OF DAILY ADMINISTRATION OF SODIUM SALICYLATE 50 GRAINS AND SODIUM BICARBONATE 100 GRAINS ON THE EXCRETION OF VITAMIN C IN THE URINE OF 15 OF THE CONTROL CHILDREN (TABLE 1).

Average excretion of ascorbic acid per 24 hours in control period = 12·2 mgm.
Range = 4·5 — 35·7 mgm.

Average excretion of ascorbic acid per 24 hours during salicylate therapy = 15·9 mgm.
Range = 6·7 — 50·7 mgm.

Another factor that was considered to be worth investigating was that of fever. A number of children suffering from active chorea were treated with injections of typhoid vaccine and an artificial fever thus induced. The method of Sutton (1933) was used with increasing daily doses. The temperature reaction reached 103°–104° F. in one to two hours and then gradually subsided to normal. The average daily excretion of ascorbic acid was estimated before and during this treatment and the results are recorded in table 7. The average output before treatment was 13·0 mgm. in twenty-four hours. The average daily excretion during fever treatment was 14·7 mgm. This is a slight but definite increase and would indicate that the presence of fever will augment the daily excretion of vitamin C in the urine. Nearly all the cases of acute rheumatic fever referred to in table 4 had some elevation of temperature at the time of collection of specimens of urine, but it was not elevated to the degree obtained by typhoid vaccines. On the other hand, the artificially induced fever only lasted for two or three hours out of the twenty-four.

TABLE 7

THE EFFECT OF FEVER INDUCED BY TYPHOID VACCINE ON THE EXCRETION OF VITAMIN C IN THE URINE

CASE	AVERAGE DAILY EXCRETION BEFORE TREATMENT (3 DAYS)	AVERAGE DAILY EXCRETION DURING FEVER THERAPY (5 DAYS)
1.	9·4 mgm. ascorbic acid.	15·3 mgm. ascorbic acid.
2.	2·8 ,, ,, ,,	5·0 ,, ,, ,,
3.	16·3 ,, ,, ,,	15·3 ,, ,, ,,
4.	9·9 ,, ,, ,,	19·4 ,, ,, ,,
5.	23·0 ,, ,, ,,	15·8 ,, ,, ,,
6.	16·6 ,, ,, ,,	17·4 ,, ,, ,,
	Average = 13·0 mgm.	Average = 14·7 mgm.

Comment

The study of infants suffering from scurvy by means of the urinary estimation of vitamin C has shown there is a marked diminution in the daily excretion of ascorbic acid even when quantities are administered by mouth, but for the diagnosis of this disease it is necessary still to depend on the clinical and radiological findings rather than the excretion of the vitamin. This is even more true since the recent studies of Park (1935) and co-workers, who have pointed out in detail the earliest radiological changes of scurvy. The same may be said for the recognition of the various stages in the healing process ; the skiagrams indicate the progress of the patient more acurately than do the biochemical estimations of vitamin C in the urine.

In the course of this investigation a number of interfering factors producing variations in the excretion of vitamin C in the urine have been studied. Some of these have already been referred to in the recent literature. Medication in rheumatic fever was found to increase the excretion of ascorbic acid. Elevation of temperature appears to have a less obvious effect. Infection definitely diminishes the stores of vitamin C in the body and tends to produce minor degrees of deficiency. The acidity or alkalinity of the urine affecting the excretion of ascorbic acid has been investigated by Hawley and Stephens, and they have suggested that there are probably several other unknown factors that interfere with the correct evaluation of these tests. Absorption and utilization are among these.

Parsons (1938) in the Withering Lectures discusses some of the factors producing variations in the excretion of vitamin C. He points out that the error due to certain interfering substances in the urine can be eliminated when testing for vitamin C by doing two separate estimations. An ordinary estimation is done and one after warming with a small amount of copper sulphate to destroy the vitamin, and the difference between the two results indicates the full amount of ascorbic acid excreted. This was not done in this study, but it seems possible to draw certain general conclusions from the comparative results obtained in this investigation. The presence of infection in the body will frequently diminish the stores of vitamin C, thus gradually reducing the average daily output and the response to test doses. This has been borne out by all recent investigations. In this series, the rheumatic fever patients did not show this to the same extent as other types of infection. The response to test doses indicates some deficiency, but the daily output was increased. When these patients were investigated two or three months later in the convalescent home, they showed no deficiency either in daily output or response to test doses. The average daily output was almost the same as the age group six to thirteen years in the controls (table 1). The rheumatic patients were in this age group and therefore should be compared with them. The high values recorded in this paper for excretion of vitamin C in the acutely active stage of rheumatic fever may be the result of several factors mentioned previously. They are considerably higher than those reported by Abbasy (1936), but it may be that

the patients studied here were in a more acute phase of the disease. Again the two series are not exactly comparable, because these results have not been related to body weight as was done by Abbasy and co-workers.

The results of this investigation support those of Sendroy and Schultz (1936), Perry (1935) and others, who found no direct evidence to support the concept that rheumatic fever is a manifestation of a deficiency of vitamin C. The conclusions reached by Abbasy and others (1936) concerning the diagnostic use of this biochemical test for vitamin C in rheumatic fever appear unwarranted by their own results, since they found the same degree of deficiency in their patients suffering from tuberculosis.

A more accurate method of determining various degrees of vitamin C deficiency may be evolved which will permit a more satisfactory interpretation of results. In spite of the great volume of work on the subject, the relation of subclinical scurvy and mild vitamin C deficiencies to the etiology and course of various diseases remains almost as vague as before the introduction of the present tests. From the results obtained in this investigation and those accumulating in the literature, it is unlikely that more than a few children over two years suffer from a deficiency of vitamin C sufficient to impair their health in any way.

Summary

An investigation has been carried out on several groups of children with and without infection to estimate the value of a biochemical test for vitamin C in the urine and study its use as an indication of various degrees of vitamin C deficiency.

The limits of the value of this test in determining the various stages of healing in a case of scurvy have been discussed.

A group of thirty-nine children between the ages of two and thirteen years in the medical and surgical wards of the hospital who had little or no evidence of infection were found to have an average daily excretion of 9·7 mgm. of ascorbic acid in the urine. The older age group (seven to thirteen years) was found to have an average daily excretion of 11·5 mgm., while the average of the younger group (two to six years) was 5·5 mgm. Marked individual variations were noted.

Children with acutely active rheumatic fever were found to excrete more vitamin C than convalescent patients. The convalescent rheumatic patients excreted an amount approximately the same as controls in a similar age group.

Saturation tests revealed a slight deficiency in the stores of the vitamin in active rheumatic fever patients as compared with convalescent rheumatics or controls.

The administration of sodium salicylate (50 grains) and sodium bicarbonate (100 grains) was found to increase the excretion of vitamin C in the urine.

Artificially induced fever by the use of typhoid vaccine produced a slight increase in the excretion of vitamin C.

No direct evidence was found to support the theory that rheumatic fever is a manifestation of a vitamin C deficiency associated with an infection.

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OTITIS MEDIA AND MASTOIDITIS IN INFANCY

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Otitis media and mastoiditis occurring in infancy have long been recognized as most troublesome disorders and, of recent years, would appear to be receiving the attention they merit. The frequency of otitis media or otitis media and mastoiditis found both in the infants' wards and in the autopsy room of the Alder Hey Children's Hospital has led to this statistical and clinical enquiry into this common and frequently lethal occurrence.

Of the 1,324 infants under one year admitted to this hospital during the year 1936, 195 (14 per cent.) suffered at one time or another from otitis media or otitis media and mastoiditis. In a certain proportion the ear infection was undoubtedly secondary to some other pathological process. The remainder were cases in which the ear infection appeared to be responsible for the child's illness and in which, in the majority, suitable treatment of the ear resulted in improvement. This latter and more interesting group is here called ' primary.' The difficulties of making such a classification will at once be apparent, and any case which seemed in any way doubtful has been included in the secondary group. The greatest difficulty was encountered in those associated with nutritional defect. A recent otitis occurring in an infant who had been under observation for some time for hypothrepsia or athrepsia was considered as secondary. A comparatively long history of otorrhoea or otitis and more recent failure to gain in weight was regarded as probably ' primary otitis.' Doubtful cases were placed in the group of secondary otitis. Some of these were perplexing.

For example, a hypothreptic child was admitted with a history of insufficient feeding for the past five weeks. At first the tympanic membranes showed lack of lustre and nothing else. After two weeks, during which the infant was ill, fretful, pyrexial and vomiting, the tympanic membranes showed more definite

signs of inflammatory change and otorrhoea began with improvement in the general condition. Although the acute symptoms subsided and the feed was suitable, the infant still did not gain weight and the ears continued to discharge profusely. Is the otorrhoea secondary to the under-nourished condition, or is the hypothrepsia secondary to the otitis, or is it a vicious circle ?

Analysis of cases

The results of an analysis of the cases of secondary otitis media and mastoiditis are as follows :—

I. Secondary otitis media

1. ASSOCIATED WITH RESPIRATORY INFECTIONS

Of the seventy-four patients, fifty-four recovered and twenty died. Seven were operated upon and of these three died. The percentage mortality for this group was 27.

2. ASSOCIATED WITH NUTRITIONAL DISTURBANCE

Of the twenty-one patients, eleven recovered and ten died. Four were operated upon and of these three died. The percentage mortality for this group was 47.

3. ASSOCIATED WITH OBVIOUS NASOPHARYNGITIS, BUCCAL INFECTION OR DEFORMITIES

Of the twelve patients, eight recovered and four died. The percentage mortality for this group was 33.

4. MIXED GROUP (nine patients of whom four died (D.)).

Otitis media—associated with faucial diphtheria (D.).
" cretinism.
" scalds of leg.
" severe conjunctivitis.
" abscess of eyelid.
" congenital hydrocephalus (D.).
" meningitis (D.).
" birth cerebral haemorrhage and atelectasis (D.).
" cervical abscess.

SUMMARY OF PREVIOUS BREAST FEEDING OF SECONDARY GROUP

GROUP	MORE THAN 3 MTH.	1–3 MTH.	NONE OR LESS THAN 1 MTH.	ENTIRELY BREAST FED	NO. UNDER 9 MTH.	TOTAL NO. OF CASES
(1)						
Respiratory	11	13	31	3	55	74
Mortality, per cent. ..	36	23	32	nil	31	27
(2)						
Nutritional	1	10	9	1	20	21
Mortality, per cent. ..	100	40	55	100	50	47
(3)						
Nasopharyngitis, etc. ..	4	3	4	1	11	12
Mortality, per cent. ..	25	33	50	nil	36	33

OBSERVATIONS ON SECONDARY GROUP.—In the group associated with respiratory infections the greatest number of cases and the highest death rate (31 per cent.) occurs in the age group 3–9 months, while in the group associated with nutritional disturbance the greatest number occurs in the age group 0–6 months, i.e. the earlier months of life, with a death rate in this group of 45 per cent. In the group associated with nasopharyngitis, the greatest number is in the age group 0–6 months. The previous feeding of these children does not appear to influence the results noticeably.

II. Primary otitis media and mastoiditis

The ' primary ' group has been sub-divided as follows :

(A) CLASSICAL MASTOIDITIS.—This sub-group includes those instances in which the child was admitted with mild constitutional disturbance, a history of otorrhoea, evidence of pain in the ear shown by restlessness and rolling of head, with redness, swelling and oedema over the mastoid process, i.e. signs of exteriorization. There were seven such patients, among whom the other ear was involved in four.

Treatment was by operation.

(B) OTITIS MEDIA AND LATENT MASTOIDITIS.—Here are included those cases in which the child showed signs of obvious otitis media, often without mastoiditis, and cases with or without local signs of otitis media, and involvement of the mastoid process without signs of exteriorization. This group has been divided further into :

I. Very toxic. These patients were admitted with a history of diarrhoea and vomiting, usually only of a few days' duration, some loss of weight, refusal of feeds, rolling of head, screaming attacks, fretfulness, drowsiness and, in a few, convulsions. It is noteworthy that in only three cases of this group was there a history of otorrhoea. On examination these infants were found to be dehydrated, grey and toxic, and in the majority toxicity was much more pronounced than dehydration. The fontanelle was depressed and the stools green, loose and frequent. Some had high temperatures, some moderately elevated and some subnormal. Some infants, admitted in fair condition, rapidly became very ill and toxic. Examination of the ears showed tympanic membranes acutely inflamed and bulging, dull red, mildly injected or apparently normal. In some cases myringotomy released pus with improvement in the general condition and fall in temperature. In others only serous fluid was obtained on myringotomy, but within forty-eight hours pus was discharging freely. In one case the tympanic membranes appeared normal throughout, the infection of the middle ears and mastoid processes being discovered at autopsy; in another no pus was obtained at myringotomy, but at the autopsy pus was found in both mastoids, the middle ears being relatively clear. In another both tympanic membranes seemed normal, and later both middle ears discharged spontaneously. In yet another, with a brief, acute history, the child

was admitted practically moribund with greyish tympanic membranes, and in the slender hope of averting a fatal issue bilateral posterior drainage was performed and thick pus found in both mastoids.

The treatment of this group comprised :—(1) Local : instillation of guttae acidi carbolici et glycerini (1 per cent.) ; local heat was applied and myringotomy performed if necessary. (2) General : parenteral fluid by the subcutaneous, intravenous or intra-peritoneal route. In the early stages these children were fed on skimmed lactic acid milk and later, as tolerance increased, on lactic acid milk formulae with varying percentages of glucose. (3) Operative : of the thirty-three cases in this group, ten were operated upon and of these eight died.

II. Mild cases. These patients were mildly ill in the sense that there was no toxicity, no dehydration and the constitutional disturbance was not marked. They were admitted with or without history of otorrhoea, sometimes unilateral, sometimes bilateral and usually ultimately bilateral. Some suffered from diarrhoea and vomiting, some did not. Screaming, restlessness, head rolling, fretfulness were common symptoms and in one or two there was a history of constipation. The temperature was sometimes elevated and sometimes normal. On examination, the general condition of these infants was good without signs of toxicity or dehydration, and no physical signs were discovered except in the ears. The tympanic membranes were sometimes inflamed and bulging, slightly injected or merely lacked lustre. Some had myringotomy performed and some discharged spontaneously. In this group 33·3 per cent. had discharging ears on admission, 25·6 per cent. were assisted by myringotomy unilateral or bilateral, 20·5 per cent. discharged spontaneously and 20·5 per cent. settled with local medical treatment and no surgical intervention.

The treatment was as follows :—(1) Local : guttae acidi carbolici et glycerini (1 per cent.) or a mixture of guttae acidi carbolici et glycerini and spiritus vini rectificatus, or the spiritus vini rectificatus (60 per cent.) alone. Myringotomy was performed if necessary. (2) General : these patients were always put on a feed of suitable caloric value, as intolerance to food was rarely present. (3) Operative : of the thirty-nine cases in this group, four were operated upon and all four recovered. One of these had bilateral posterior drainage, the others unilateral. Those operated upon had persistent otorrhoea with improvement in the general condition as evidenced by satisfactory taking of feeds and gain in weight.

Based upon the classification thus outlined the ' primary ' group can be analysed in more detail as follows :

A. CLASSICAL MASTOIDITIS

There were seven such cases, of whom four were of normal weight and three were hypothreptic. All seven recovered. With regard to the previous feeding of the seven cases, five were under nine months, and only one had more than three months' breast feeding, two more than a month and two less than a month. Subsequent bottle feeding was on the whole good. Three had full vitamins, one vitamin C, one none.

B. OTITIS MEDIA AND LATENT MASTOIDITIS. (I) VERY TOXIC GROUP

AGE GROUP AND NUTRITIONAL CONDITION	NO. OF CASES	RECOVERED	DIED	OPERATION R.	OPERATION D.	P.M.	MORTALITY, PER CENT.
0–3 months, N.	4	1	3	—	2	1	
H.	2	—	2	—	1	1	
A.	5	—	5	—	—	3	
Totals	11	1	10	—	3	5	90
3–6 months, N.	9	3	6	2	3	1	
H.	4	—	4	—	1	1	
A.	—	—	—	—	—	—	
Totals	13	3	10	2	4	2	76
6–9 months, N.	2	—	2	—	—	1	
H.	6	1	5	—	1	2	
A.	—	—	—	—	—	—	
Totals	8	1	7	—	1	3	87
9–12 months, N.	—	—	—	—	—	—	
H.	1	—	1	—	—	1	
A.	—	—	—	—	—	—	
Totals	1	—	1	—	—	1	100
Grand Total	33	5	28	2	8	11	84·8

N.—Normal weight or within 20 per cent. of normal weight.
H.—Hypothrepsia : 60–80 per cent. of normal weight.
A.—Athrepsia : less than 60 per cent. of normal weight.
R.—Recovered.
D.—Died.

B. (II) MILD CASES

There were thirty-nine such cases, of whom all recovered.

SUMMARY OF PREVIOUS BREAST FEEDING OF PRIMARY GROUP

GROUP	MORE THAN 3 MTH.	1–3 MTH.	NONE OR LESS THAN 1 MTH.	ENTIRELY BREAST-FED	NO. UNDER 9 MTH.	TOTAL NO. OF CASES
(i) Very toxic	4	8	20	2	32	33
Mortality, per cent.	25	87	95	100	84·3	84·8
(ii) Mild cases	5	10	13	3	28	39

SEASONAL INCIDENCE OF PRIMARY GROUP

MONTHS OF YEAR	ALL CASES	TOXIC GROUP	MILD GROUP	CLASSICAL GROUP
January	3	1	1	1
February	3	0	3	0
March	3	0	2	1
April	2	1	1	0
May	5	0	3	2
June	6	1	5	0
July	9	6	2	1
August	10	6	4	0
September	12	4	8	0
October	15	10	3	2
November	9	3	6	0
December	2	1	1	0
Totals	79	33	39	7

Observations

As a result of clinical experience we believe that in a certain proportion of cases otitis media and mastoiditis are responsible for the diarrhoea and vomiting syndrome in infancy.

This has been the experience elsewhere, notably Ebbs et alia (1937), Le Mée (1936), Ribadeau-Dumas et alia (1936), Marriott (1935) and Jeans (1926). Spahr (1929) and Holsclaw et alia (1930) report similar findings. Johnstone, Brown et alia (1930), who have conducted an exhaustive bacteriological research, are of the opinion that ' masked mastoiditis ' is not an etiological factor in the diarrhoea and vomiting syndrome, and state that it is an enteral infection due to a variety of organisms belonging to the colon-typhoid-dysentery group.

It is striking that a majority of the cases in the toxic group occurred in babies of normal weight (fifteen cases) and a minority in the athreptic group (five cases). The relative absence of otorrhoea in the toxic group suggests that the early occurrence of the toxic picture, possibly coincident with involvement of the mastoid process, is due to pent-up infection in the middle ear and lack of satisfactory drainage. This view would appear to be supported by the improvement in the general condition—unfortunately, in the majority of cases, only temporary—which followed myringotomy and release of pus from the middle ear. The absence of otorrhoea is also a strong plea for the routine otoscopic examination of the tympanic membranes in cases presenting this distressing clinical picture, although, as Ebbs (1937) points out, the results of this examination may leave the clinician in considerable doubt. None of the mild cases which were already discharging or in which satisfactory drainage was established, either spontaneously or by myringotomy (i.e. 79 per cent.), developed signs of toxicity. It seems reasonable to suggest that the presence or early establishment of satisfactory drainage prevented the onset of the severe toxic symptoms. In classical mastoiditis, when infection becomes exteriorized, as indicated by redness, swelling and oedema over the mastoid process, symptoms of toxicity did not arise. Unfortunately this happy outcome is relatively infrequent.

In the group of classical mastoiditis there were no deaths. In the toxic group the death rate is regrettably high (84·8 per cent.) and the highest death rate appears to be in the age group 1–3 months. It is unfortunate that there was only one case in the age group 9–12 months, as this is possibly a misleading figure. In the mild group there were no deaths.

It is frequently stated that breast feeding, whenever possible, is a mother's best method of ensuring her child's successful avoidance of infection, and the results of the present analysis would appear to some extent to bear out this statement. Among the patients with classical mastoiditis only one had more than three months' breast feeding, while the remainder all had shorter periods. In the toxic group, leaving out of consideration for the moment the two entirely breast-fed infants who both died, it will be seen that the highest death rate occurs amongst the infants with no or less than one month's breast feeding, and in the mild cases the greatest number occurs amongst those with no or less than one month's breast feeding.

The results of operative interference are interesting, as, if an attempt is made to classify these cases according to operative results, they are found to fall into the three groups of the suggested classification :

(1) Classical mastoiditis—when operation is always indicated and the results good.

(2) Very toxic group—when the results are poor.

(3) Mild group—when the results are good in selected cases.

The French authorities (Le Mée, 1936 ; Ribadeau-Dumas, 1936) report satisfactory results from the operation of antrotomy on cases corresponding to those in the toxic group of the present series. We are unable to confirm this experience, as 80 per cent. of such cases operated upon died and 86 per cent. of those not operated upon died. We feel that once the infant's infection so overwhelms it as to produce symptoms of toxicity, its chances of survival are just as great with conservative treatment as with surgical interference.

It will be seen from the analysis of the seasonal incidence of the primary group that the greatest numbers occur during the months of July, August, September and October, the season of the year when diarrhoea and vomiting are most prevalent in infancy.

Summary

(1) An analysis of cases of otitis media and mastoiditis occurring in children under one year, admitted to the Alder Hey Children's Hospital during the year 1936 is made and classification is suggested as follows :—

I. Secondary.
   1. Otitis media associated with respiratory infections.
   2. Otitis media associated with nutritional disturbance.
   3. Otitis media associated with nasopharyngitis, etc.
   4. Mixed group.

II. Primary.
   A. Classical mastoiditis.
   B. Otitis media and latent mastoiditis.
      1. Toxic cases.
      2. Mild cases.

(2) Symptoms and treatment of the primary group are described in detail, and summaries of previous feeding of both groups are given.

(3) Results of operation in the primary group are commented upon, and the conclusion drawn that the cases in which satisfactory operative results are likely are those of classical mastoiditis and mild cases with chronic otorrhoea in which the infant's general condition is good or is rendered good by general treatment.

(4) An analysis of the seasonal incidence of primary otitis media and mastoiditis is given.

(5) Confirmation is afforded for the theory already advanced by numerous authors that the well-known ' diarrhoea and vomiting syndrome ' is frequently caused by the presence of otitis media and latent mastoiditis, the pathology of

which is of the nature of a retention phenomenon with lack of satisfactory drainage.

We wish to acknowledge our indebtedness to Dr. W. E. Crosbie, Medical Superintendent, Alder Hey Children's Hospital, Liverpool, for permission to publish this work, and to Dr. Norman B. Capon for his helpful advice and criticism.

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RADIOLOGY IN THE DIAGNOSIS OF HYPERTROPHIC PYLORIC STENOSIS

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Most text-books on paediatrics mention the employment of radiology in the diagnosis of hypertrophic pyloric stenosis. There is, however, little evidence of unanimity not only concerning its value in this direction but also regarding the precise diagnostic indications to be gained by this particular method of investigation.

Paterson (1937), for example, merely states that ' resort to x-rays settles the diagnosis definitely ' without giving any idea of the special features which are of diagnostic importance. Pearson and Wyllie (1935) can also be classed with those who believe that radiology is of considerable value in the diagnosis of hypertrophic pyloric stenosis, since they write that by its use ' pyloric stenosis, if present, can usually be demonstrated.' These latter writers do admit, however, that this method of investigation is ' not generally a necessary procedure for diagnosis, but,' they continue, ' it is of value as an aid to the differential diagnosis of pyloric stenosis and pylorospasm.' The sole diagnostic indication from the radiological point of view given by Pearson and Wyllie is that in ' stenosis little or nothing leaves the stomach for hours,' since ' normally immediately after a meal food begins to leave the stomach, which is completely emptied in three hours.' Sheldon (1937) is another author who gives almost similar diagnostic indications, since he writes that ' the stomach (in hypertrophic pyloric stenosis) is not empty after three or four hours.' Teall (1933) also considers that ' the results of the radiological investigation in infantile pyloric stenosis are reliable ' and gives as the diagnostic features, ' no passage of the meal into the duodenum within $\frac{1}{4}$ hour ' and ' the opaque meal remaining in the stomach for six hours.' Parsons and Barling (1933) speak of the radiological examination being valuable in two ways, viz. by providing ' an accurate idea of the size of the stomach ' (although the real use of this information is not stated), and in addition by being the ' best means of observing the rate of emptying of the stomach ' (but the degree of delay which is indicative of stenosis is not mentioned).

Some writers are less enthusiastic concerning this aid to the diagnosis of pyloric stenosis and, while they admit that the radiological investigation may have some value, they do not consider it necessary.

Richter (1924), for example, speaks of it only being confirmatory and deprecates ' its routine use, as it leads to unnecessary delay ' in instituting treatment. Neff (1927) advises that the radiological examination should only be carried out early in the disease, when, apparently, he considers the real difficulties in diagnosis arise. Griffith and Mitchell (1937) only see a value in such investigations in ' differentiating pyloric stenosis from oesophageal conditions,' a difficulty, however, which could be more easily and just as certainly overcome by the use of the oesophageal tube.

And, finally, there are authors who consider radiology of little or no diagnostic value.

Grulee and Bonar (1926) say that ' x-ray is not a great help in doubtful cases and the diagnosis can be made without it in the more doubtful ones,' and F. M. B. Allen (1930) writes, ' opaque meal examination is not worth the labour, as the result is most unreliable and may even confuse the issue more than illuminate it.'

It is interesting to contrast with the above views of the clinician those expressed by the radiologist. It would seem, however, that the radiologist as a rule has been more concerned with affirming the presence of the condition than with deciding upon its absence, at least judging by the diagnostic indications which he formulates.

For example, Cecil H. Bull (1935) states that ' food does not leave the stomach for two hours and remains in the stomach in a true case of hypertrophic pyloric stenosis indefinitely.' Hotz (1933) in his discussion of the subject refers to the thickness of the stomach and ' delay in emptying up to twenty-four hours.' While Köhler (1935) writes, ' If within an hour the stomach of a newly-born child has not allowed any of the contrast meal to pass through the pylorus—which normally happens at once—there is as a rule a congenital hypertrophic stenosis of the pylorus present, even though no corresponding tumour can be palpated.'

While I am one of those physicians who believe that radiology is quite unnecessary for arriving at a diagnosis of hypertrophic pyloric stenosis and that the pathognomonic feature—the pyloric tumour—can be palpated in all the cases, I recently submitted to a radiological examination after a barium meal a series of examples of this disease, and as controls a number of infants who appeared quite healthy or were suffering from vomiting, but in whom no pyloric tumour could be felt. The object was to discover what value, if any, this method of investigation really possessed, and it is the findings obtained during this study which form the subject of the present communication.

Method

The same procedure was employed in all the cases. As soon as the child came under observation and a diagnosis was made, a ' plain skiagram ' was taken. Thereafter, a barium meal (milk and chocolate barium amounting to

two-and-a-half to three ounces) was given by bottle or spoon and pictures taken immediately, one quarter of an hour, half an hour, three quarters of an hour, one hour, two hours, three hours, four hours, five hours, six hours, seven hours and on one occasion eight hours after the completion of the feed. In some of the examples of pyloric stenosis the examination was repeated after the symptoms had disappeared, either as the result of operation or medical measures, and the child had apparently recovered.

Results

Details of the findings are given in the table (p. 152) and in charts I and II. The course of the investigation has been divided into two periods, (*a*) during

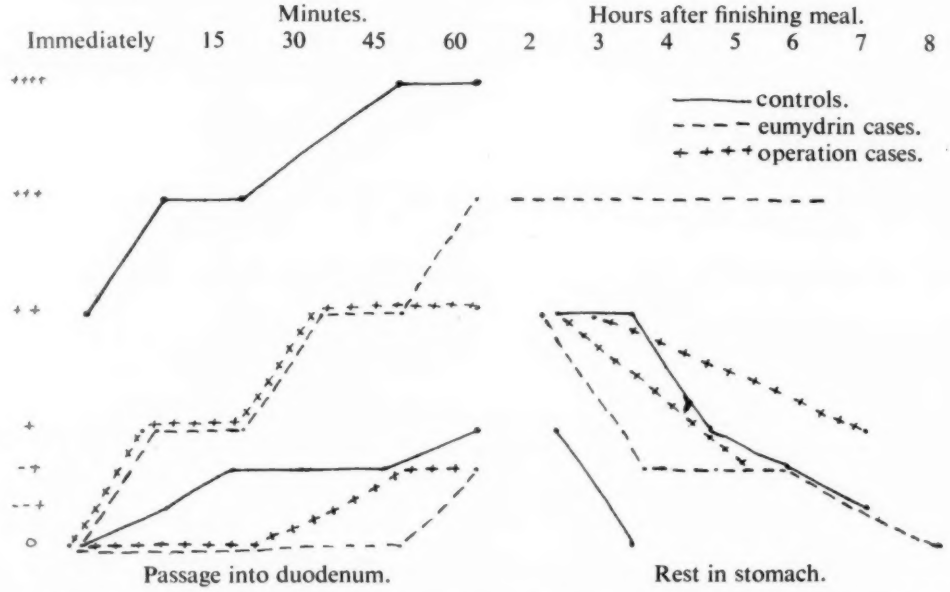

CHART I.—Chart showing the maximum and minimum rates of emptying of stomach with and without hypertrophic pyloric stenosis.

——— normal.
– – – – – hypertrophic pyloric stenosis treated with eumydrin.
++++ hypertrophic pyloric stenosis treated by operation.

the first two hours after ingestion of the meal, and (*b*) from two hours after ingestion onwards. In the first period attention was directed to the passage of the meal through the pylorus and this is indicated in the table and on the charts by + and − signs. During the second period it is the amount of the meal still retained in the stomach which is indicated by the + and − signs. It was thought that in this way the best idea of the complete cycle of ' gastric motility ' would be provided.

The skiagrams obtained in a typical example of pyloric stenosis and in one of the control group of children are reproduced on pp. 155 and 156. For these pictures I am indebted to Dr. Calthrop, Honorary Radiologist to the Princess Elizabeth of York Hospital for Children.

A scrutiny of both the table and the charts shows that in the absence of hypertrophic pyloric stenosis, the opaque meal as a rule begins to leave the stomach immediately, and that within thirty to forty-five minutes a considerable amount of the meal has entered the small intestine. Sometimes, however, in the absence of stenosis food does not leave the stomach immediately, and even by the end of an hour after ingestion comparatively little may have entered the duodenum. On the other hand, in hypertrophic pyloric stenosis it is usual for the passage of the meal into the small intestine to be delayed, but even in undoubted examples verified by operation, the opaque meal may enter the duodenum as soon, and at the same rate, as in the normal child. Thus from

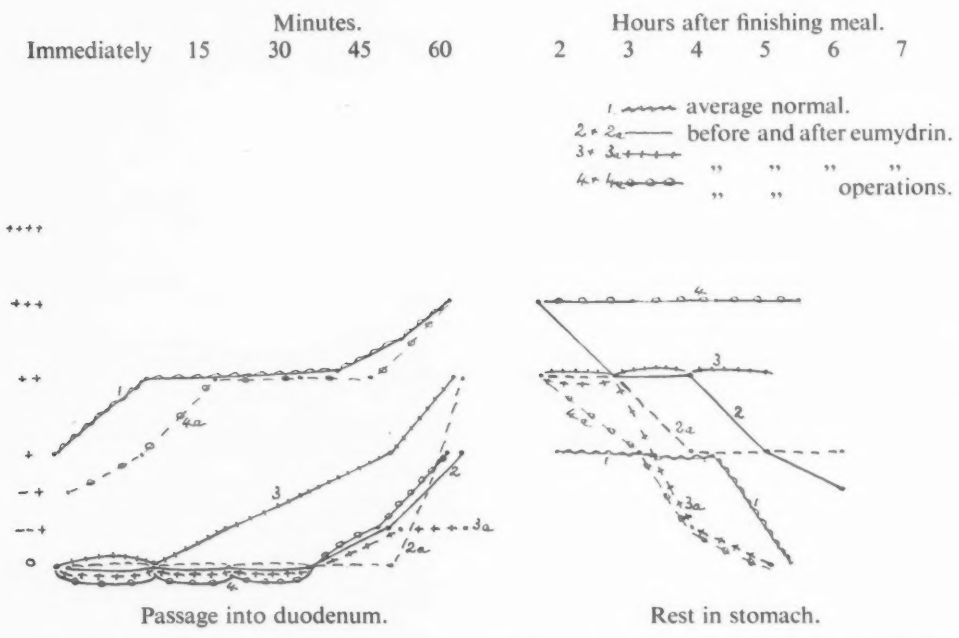

CHART II.—Graphic representation of rate of emptying of the stomach before and after recovery from hypertrophic pyloric stenosis.

this aspect of the investigation there is no sharp line of distinction between the case with pyloric stenosis and the one without pyloric stenosis.

It is also apparent from the table and charts that there exists, so far as the time required for complete emptying of the stomach is concerned, the same great variations in both the normal stomach, and in the presence of hypertrophic pyloric stenosis. In my experience the normal stomach is not usually completely empty until five or six hours after the ingestion of the opaque meal, and in the presence of hypertrophic pyloric stenosis until six or seven hours after ingestion. On occasion, however, complete emptying of the normal stomach may be delayed till eight hours after the meal, whereas the stomach with undoubted hypertrophic pyloric stenosis may be practically empty by the fifth hour, thus again revealing the overlap which deprives this method of investigation of any diagnostic value.

Some authors mention evidence of hyperstalsis during the period of observation as being of importance in indicating the presence of stenosis, but in my experience this is not an invariable feature in the skiagrams and is seen almost as frequently in the normal as in the abnormal case.

Discussion

When the variations in the severity of the symptoms in this condition are remembered, it is quite understandable how there should not be any sharp line of distinction between the case with stenosis and the case without stenosis. Nevertheless, it might be suggested that this method of examination would still provide a readier means of recognizing those more severe examples which require immediate surgical treatment than is possible by paying attention to the faecal output and the general appearance of the patient. My experience, however, has not lent any support to such a contention. For some time past it has been my practice to institute medical measures as a routine and only to resort to surgical intervention when this seemed the only means of saving the child. In the table and in the charts it is indicated whether pyloric stenosis was or was not present, and if present what method of treatment was adopted. The findings show definitely that there was much greater interference with the motility of the stomach in some cases which responded to medical measures than in others which ultimately required surgical intervention. Indeed, in one case (no. 2) the symptoms were so slight that I recorded it in detail (Findlay, 1937) as an instance of pyloric stenosis without symptoms, and yet radiologically it is one of the most marked examples of the series.

In this connexion it is interesting to contrast the behaviour of the motility of the stomach in this condition at the height of the symptoms and after recovery when all symptoms had disappeared. The findings are noted in the table and in a few typical examples are graphically represented in chart II. A difference between the findings in this respect according to whether the treatment had been medical or surgical might be expected. As a result of surgical intervention all constriction of the pyloric canal is removed at once and consequently an immediate and marked improvement in conditions would be anticipated, and such is indeed what occurs. In those cases in which a barium meal was performed three or four weeks after operation the emptying rate, as judged by the passage of the meal into the duodenum and by complete emptying of the stomach, had returned to the normal. But this was not so in the examples treated medically, since even as long as six to eight weeks after all symptoms had disappeared the typical radiological picture of pyloric stenosis persists. This suggests that there are two factors causing the obstruction: spasm of the muscle (which is relieved by medical measures) and narrowing of the pyloric canal from the mass of the hypertrophied muscle (which is rectified by Rammstedt's operation). It is interesting to note that of the two examples treated medically (no. 2 and 3 in chart II) one (no. 2) showed practically no change after the symptoms had disappeared, whereas the other (no. 3) revealed an even

slower passage into the duodenum after recovery, but an ultimate emptying rate which compared favourably with the normal child. These are findings which still further support the contention that radiological investigation is of no value in differentiating the case requiring immediate operation from the one which would recover by the adoption of medical measures.

Meuwissen and Sloff (1932) also came to the conclusion that dilatation of the stomach, increased peristalsis, delay in passage of the meal into the duodenum or delay in complete emptying of the stomach were unreliable as guides to the diagnosis of hypertrophic pyloric stenosis, because all these features may be present when no stenosis exists. For these workers the only reliable radiological feature is a lengthening of the pyloric canal. This normally has a maximum length of 4 mm., whereas in hypertrophic pyloric stenosis it is invariably four or five times as long.

For the demonstration of this characteristic the Berg technique is necessary, but this, it must be remembered, involves an amount of exposure which is not without danger in the young infant. Certainly the skiagrams which these authors reproduce in their communication support their contention, but in the few instances in which we have attempted to emulate their example we were quite unsuccessful. However, apart from the danger of this type of examination, it absorbs an amount of time which, at least from the practical point of view, is quite unwarranted, for, a pyloric tumour, which is pathognomonic of hypertrophic pyloric stenosis, can invariably be detected.

Summary

(1) The current opinion regarding the value of radiology in the diagnosis of hypertrophic pyloric stenosis is discussed.

(2) The findings after a barium meal in twelve examples of hypertrophic pyloric stenosis and in twelve ' normal ' children are described.

(3) While the motility of the stomach in hypertrophic pyloric stenosis is shown to be as a rule impaired, this is not the invariable rule. In some cases of hypertrophic pyloric stenosis the motility is as good as in the normal stomach.

(4) When the time involved in this method of examination and the variability of the findings are considered, the only justifiable conclusion is that it has no place in the diagnosis of hypertrophic pyloric stenosis.

(5) The most reliable evidence of hypertrophic pyloric stenosis is the presence of a tumour, which is palpable in all cases.

Thanks are due to Dr. Calthorp for his co-operation and permission to reproduce the skiagrams of the barium meals, and to Dr. Chodak Gregory for the observations on Case No. 21.

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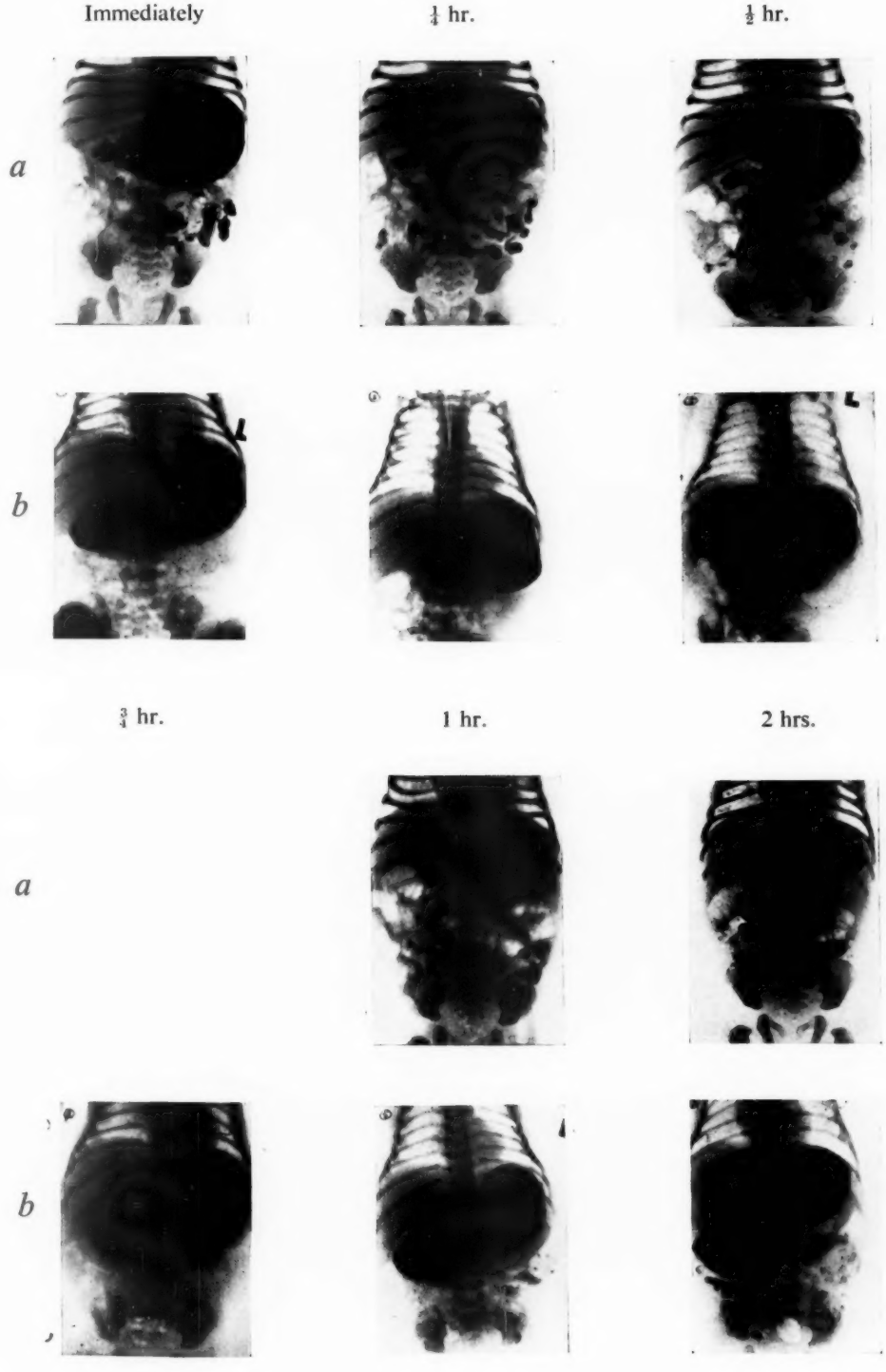
NO.	SEX	AGE, WEEKS	CONDITION	URINARY CHLORIDES, GM. PER CENT.	TREATMENT	BARIUM MEAL											
						PASSAGE INTO DUODENUM						RESIDUE IN STOMACH					
						MINUTES					HR.	HR.					
						IMMED.	15	30	45	60	2	3	4	5	6	7	8
1	F.	5	Nil.	0·22	—	0	+	+				+	+	+	−		
							+	+							+		
								+									
2	M.	4	Hyper. pyl. stenosis.	0·24	Eumydrin.	0	0	0	0	−	+	+	+	+	+	−	
										−		+	+	+		+	
										+							
	,,	12	,, ,,	0·21	—	0	0	−	−	−	+	+	+	+	+	+	
								−	−	−		+	+				
								−	+	+							
3	,,	6	Nil.	0·44	—	0	+	+		+	+		−				
							+	+		+	+		+				
										+	+						
											+						
4	,,	7	Hyper. pyl. stenosis.	0·04	Eumydrin.	0	0	−		+	+	+	+	+	+		
								−			+		+		+		
	,,	13	,, ,,	0·23	—	0	0	0		−	−	+	+	−	−		
										−	+		+	+			
											+						
5	F.	14	,, ,,	0·06	Operation.	0	−		+		+		+	−			
							−		+		+		+	+			
							+										
6	M.	11 days	,, ,,	0·26	,,	0	+	+	+	+	+		+			+	
									+	+	+		+				
7	,,	11	,, ,,	0·09	,,	0	0	0		−	−	+	+				
										+		+	+				

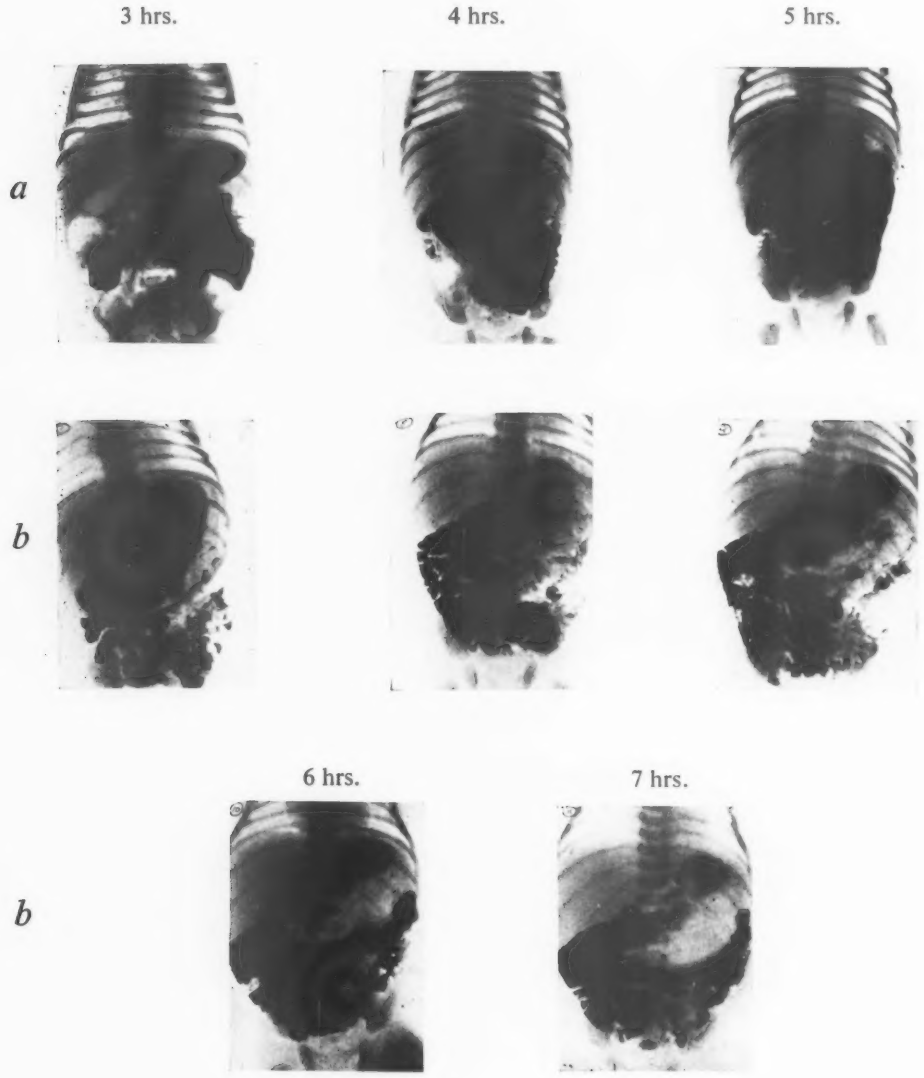
| | | |

NO.	SEX	AGE, WEEKS	CONDITION	URINARY CHLORIDES, GM. PER CENT.	TREATMENT	BARIUM MEAL											
						PASSAGE INTO DUODENUM						RESIDUE IN STOMACH					
						MINUTES					HR.	HR.					
						IMMED.	15	30	45	60	2	3	4	5	6	7	8
18	F.	40	Nil.	0·28	—	0	− − +	+	+ +	+ + +	+ + +	+ +	+ +	+	− +	− − +	
19	,,	7	Nil.	0·24	—	+	+ +	+ + +	+ + +	+ + +	+ + + +	+	−				
20	M.	6	Hyper. pyl. stenosis.	0·03	Eumydrin.	− − +	− +	+	+ +	+ +	+ + +	+	+	− +	− − +	− − +	
	,,	11	,, ,,	0·32	—	0	+	+	+	+	+ +	+ +	+ +	+ +	+ +	+ +	
21	,,	7	,, ,,	0·09	Operation.	0	0	0	0	− − +	+	+ + +	+ + +	+ + +	+ +		
	,,	12	,, ,,	—	—	− +	+	+ +	+ +	+ +	+ + +	+ +	+	− + +	−			
22	,,	14	,, ,,	0·06	Eumydrin.	0	+	+	+ +	+ +	+ + +	+ +	− +	− +	− +	− +	−
23	,,	16	Vomiting.		—	− +	+ +	+ +	+ +	+ + +	+ + +	+ +	+	− +	−		
24	,,	11	Hyper. pyl. stenosis.	0·09	Eumydrin.	0	0	0	0	0	− +	+ + +	+ + +	+ + +	+ + +	+ + +	
	,,	15	,, ,,	0·23	—	0	+	+ +	+ + +	+ + +	+ + + +	+	− − +	−			

SKIAGRAMS OF PROGRESS OF BARIUM MEAL IN (*a*) NORMAL CHILD AND (*b*) HYPERTROPIC PYLORIC STENOSIS



SKIAGRAMS OF PROGRESS OF BARIUM MEAL IN (*a*) NORMAL CHILD AND (*b*) HYPERTROPIC PYLORIC STENOSIS



THE BLOOD PHOSPHORUS IN EGYPTIAN INFANTS

BY

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and M. A. ABBOUD, M.R.C.P., D.C.H.

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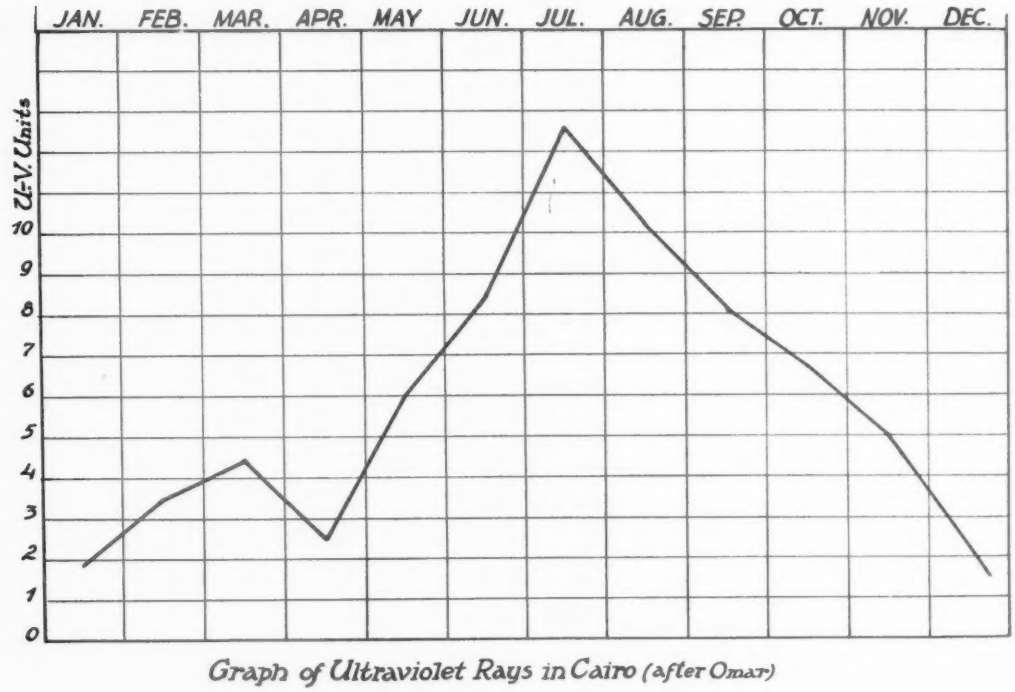
Rickets is not a new disease to Egypt. Its existence dates back to ancient times. Drawings in old Egyptian tombs show that rickets existed in the times of the Pharaohs (Ruffer, 1921). Until recently (Dicks, 1922) the disease was considered to be rare in Egypt. Shawki (1928), however, demonstrated that rickets is prevalent in this country. Nearly 50 per cent. of all Egyptian infants between the ages of six months and two years suffer from this malady. Statistics collected later by Sabri (1933*a*) showed that even in Upper Egypt, where sunshine is abundant, rickets is nearly as common as in Cairo. The possible factors concerned in the prevalence of this disease among Egyptian infants have been the subject of many recent investigations.

Milk, the basic diet of every infant, was first investigated. It was shown (Sabri and Fikri, 1932) that human, cow's and buffalo's milks (the milks commonly used for infant-feeding in Egypt) do not contain active vitamin D in any amount that can be of practical value in the prevention of rickets. On the other hand, these milks contain sufficient amounts of the precursor of vitamin D (provitamin D), which after activation by exposure to ultra-violet rays endows these milks with definite antirachitic powers. Thus, the Egyptian infant, whether naturally or artificially fed, receives most of the antirachitic factor in its milk-supply in an inactive form. Unless this factor is activated by exposure of the child to ultra-violet irradiation—obtained from natural or artificial sources—no protection against rickets is provided. There cannot be any question of lack of sunshine in this country even in the midst of the winter months. The daily average hours of sunshine during the winter season is about eight hours. Yet, in spite of these long hours of sunshine, a great part of vitamin D in human and animal milks remains in an inactive form (pro-vitamin D). These facts point to an insufficient supply of ultra-violet rays. Over-clothing, bad housing and other more or less minor factors undoubtedly play a part, but they cannot be mainly responsible for the prevalence of the disease all over the country. An insufficient content of ultra-violet rays in Egyptian sunshine appeared to us (Sabri, 1933*b*) to be the only explanation. Shawki (1928) came to similar conclusions in 1928. Estimations of the effective

ultra-violet rays worked out in 1932 (Hill's method) showed that in spite of an abundant supply of sunshine the quantity of ultra-violet rays is much below the expected. This is especially marked in the winter and spring seasons, and is ascribed to certain physical and meteorological factors (fig. 1).

Present investigations

Because of the pronounced effect of ultra-violet rays on the inorganic blood phosphorus, it was thought that a curve showing the seasonal variation of blood phosphorus in healthy Egyptian infants might further help to elucidate the etiology of rickets. Infants of an average age of six months from the Child



Graph of Ultraviolet Rays in Cairo (after Omar)

FIG. 1.

Welfare Centre and the Foundling Home of Fouad I Children's Hospital, Cairo, were investigated. Only those free from any rachitic manifestations (clinically and radiologically) were selected. The investigations were continued over a period of one year (May, 1935, to April, 1936). During this time the infants were not given any special antirachitic therapy. Blood-phosphorus estimations and skiagrams were made monthly. Those children who developed rickets or any other severe nutritional disturbance during the course of investigation were excluded.

Of two hundred infants who were investigated, only eighty-three continued to be healthy and non-rachitic. The composite blood-phosphorus curve of those infants is shown in fig. 2. The examination of this graph demonstrates two important points :

(1) There is a close relationship between the ultra-violet content of sunshine and blood-phosphorus curves of infants.

(2) During a great part of the year the blood-phosphorus level of healthy non-rachitic infants reaches a dangerously low level—4·1 to 4·3 mgm. per cent.

Comments

The influence of ultra-violet rays on the inorganic blood phosphorus is already established. It is known that the rise and fall in blood phosphorus

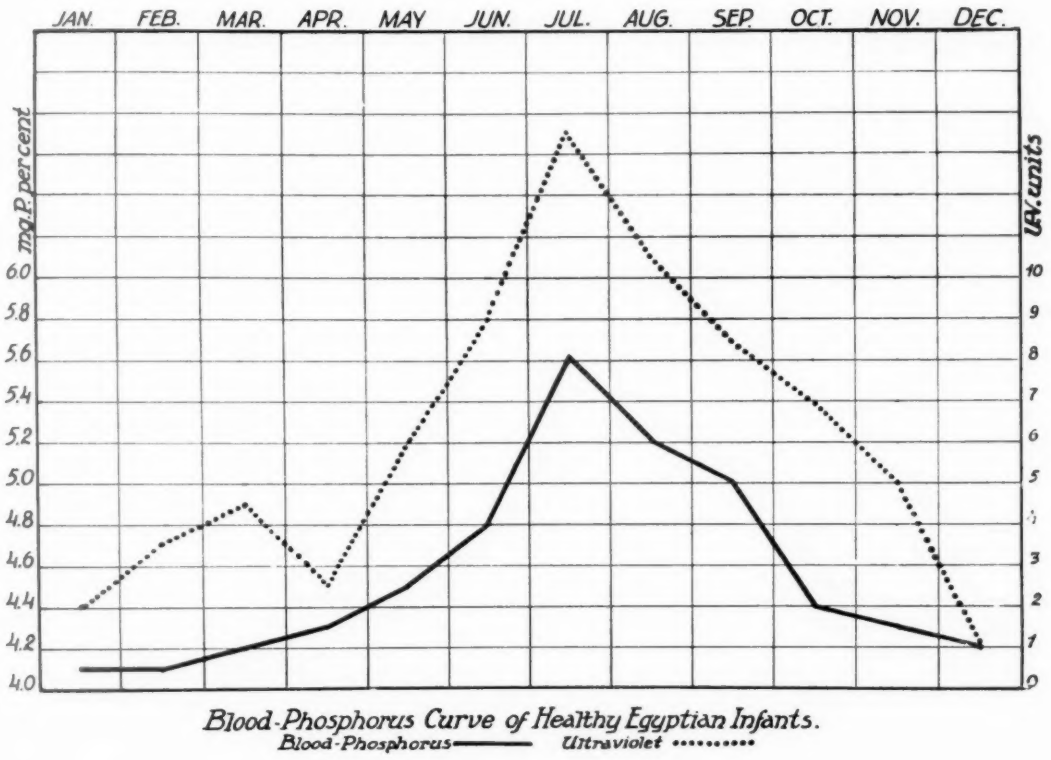


FIG. 2.

follows increase and decrease in the amount of ultra-violet rays in sunshine (Hess, 1930). This close relationship between blood-phosphorus level and ultra-violet rays is well illustrated in the present curve. The changes in the inorganic blood phosphorus which take place in rickets have already been worked out by Kramer (1933) and others, who showed that in the healthy infant, blood phosphorus lies between 4·5 and 5·5 mgm. per cent. In infantile rickets the inorganic phosphorus is reduced, and usually lies between 2 and 4 mgm. per cent. Four mgm. per cent. represents the usual dividing-point between the rachitic and normal conditions.

It will be noted from the graph that the blood phosphorus of healthy Egyptian infants falls during the winter and spring seasons to a low level—

4·1 to 4·3 mgm. per cent. ; in other words, it almost lies on the border-line between normal and rachitic conditions.

Thus, the Egyptian infant is naturally predisposed, during a great part of the year, to develop rickets. The presence of some additional factor, such as defective housing, overclothing or seclusion of the child, is sufficient to turn the balance unfavourably. It is no wonder, therefore, that rickets is so prevalent among Egyptian children.

Thanks are due to Dr. S. Naga, radiologist of Fouad I Children's Hospital, for his great help and assistance.

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OSTEOPETROSIS

BY

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The condition about to be described is known under an imposing array of names, among which osteosclerosis, osteosclerosis fragilis generalisata, marble bone or Albers-Schönberg's disease are perhaps the most familiar. The now commonly accepted name of osteopetrosis was proposed in 1926 by Karschner and means literally 'stony or petrified bones.'

The name of Albers-Schönberg is attached to this disease because he was the first to discover it radiologically in 1904. His patient was a man of twenty-four who was subsequently followed up till his death at the age of forty-nine. Similar examples were noted, however, prior to Albers-Schönberg's first description (1904) and usually labelled as leukaemia or pseudoleukaemia (Hueck, 1879 ; Neumann, 1880 ; von Jaksch, 1901). Most of the accounts of osteopetrosis appeared hitherto either in the German or American literature. One of the earliest reviews of the condition was made in 1926 by Karschner (1926), who gave a brief account of the findings in eighteen instances and added four of his own cases. Karschner's list was slightly amplified by McCune and Bradley, who published in 1934 an excellent summary of sixty-nine records including one of their own. In 1937 Harnapp produced the latest comprehensive review showing a total of seventy-nine cases, but he left out several of the less well-authenticated ones which were accepted by other authors. I was able to collect a total of 112 cases and a table of those not quoted by either McCune and Bradley or by Harnapp is given in an appendix (see p. 172).

Case record

HISTORY.—The patient, a male, aged three years and three months, is an only child of first cousins. He weighed 8 lb. 8 oz. at birth, and is supposed to have been a fortnight overdue. He sat up between six and seven months, stood up at ten months, and began to walk at fourteen months. Until about nine months the child was fed on boiled milk without the addition of any form of vitamin D ; later he was given usual mixed diet, including porridge, bone and vegetable broth, gravy and potatoes. At the age of eighteen months he was referred to me from the Ear, Nose and Throat Department, where he

attended for nasal obstruction and enlarged tonsils. At that time the boy showed somewhat enlarged epiphyses and beading of ribs with marked inspiratory indrawing of lower intercostal spaces. The tibiae were slightly curved, the skull showed marked bossing, and no teeth had yet come through. The first x-ray, although suggestive of rickets, was unusual, but in view of the findings and the history, a diagnosis of vitamin D deficiency was made. Radi-

FIG. 1.—R. P. at the age of 2 years and 10 months.

ostoleum 10 minims thrice daily was ordered, and after two months there appeared to be some improvement. The epiphyses were less widened and there was less indrawing of lower ribs, but the anterior fontanelle was as widely open as before. After another two months (July, 1936) the epiphyses felt quite normal and he cut two upper incisors. In October, 1936, he was considered fit enough for the removal of tonsils and adenoids. Following this

FIG. 2.—Skull showing enormous thickening of the base and some clubbing of posterior clinoid processes. Anterior fontanelle still open at 2 years and 10 months.

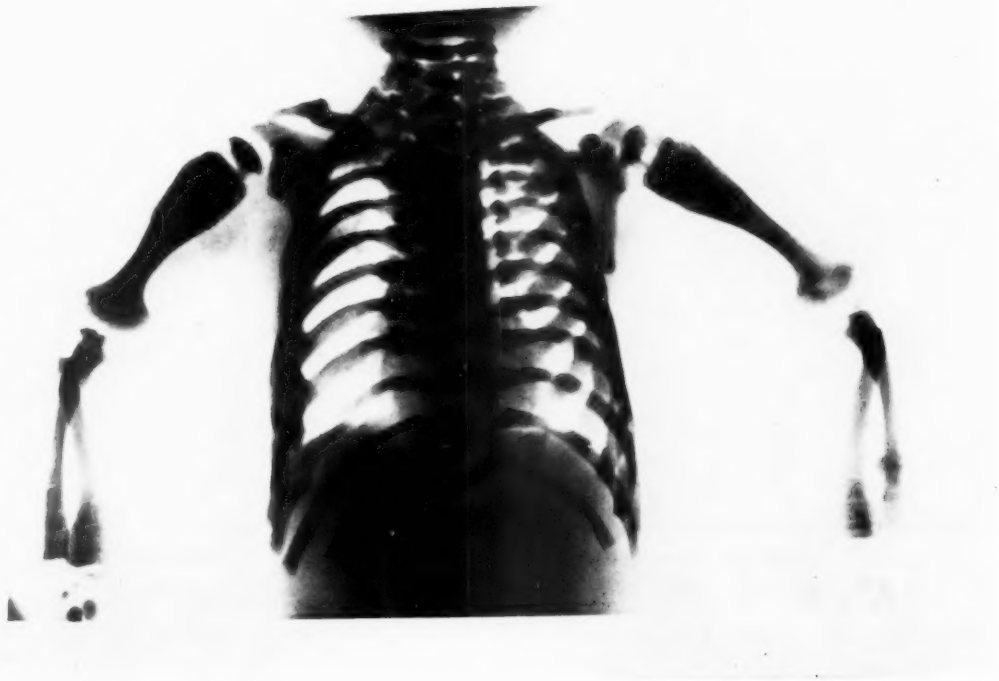

FIG. 3.—Uniform density of the whole thoracic cage. Upper ends of humeri and clubbed and an old fracture of the right clavicle can be seen.

the snuffles became less marked but he developed discharging ears for a short time.

A blood count, done on October 27, 1936, showed : Hb, 65 per cent. ; R.B.C., 4,520,000 per c.mm. ; C.I., 0·7 ; leucocytes, 23,100 ; polymorphs,

FIG. 4.—Extreme density of the spinal column and pelvis is present.

28 per cent. ; lymphocytes, 54 per cent. ; hyalines, 8 per cent. ; eosinophils, 2 per cent. ; basophils, 4 per cent. ; myelocytes, 4 per cent. The film showed anisocytosis, poikilocytosis and 1 megaloblast per 100 white cells.

In spite of the fact that adequate dosage of radiostoleum was kept up, he failed to cut any more teeth, and the fontanelle remained open as before.

Repeated x-ray examinations of the wrist showed no further evidence of rickets, and the peculiar density at the end of the bones remained unaltered. On March 20, 1937, the serum calcium was 10·5 mgm. per cent. and phosphorus 3·9 mgm. per cent.

FIG. 5.—There is clubbing and accentuation of density at the ends of the long bones, especially femora. Relatively less dense transverse bands can be seen. There is a healed fracture at the upper end of the right fibula.

He was quite normal and bright mentally and was able to say a few words before two years old. In May, 1937, his mother reported that he could only see straight in front of him and that for any outside objects he had to feel. At that time nystagmus was noted. The anterior fontanelle had been diminishing

in size gradually, and at the beginning of September, 1937, admitted only the tip of one finger. He still had only two teeth and it was thought advisable to x-ray the skull again and also the rest of the skeleton. This revealed the marked deposition of calcium in all the bones, and the diagnosis of osteopetrosis was then made.

Lately (October, 1937) the child was readmitted to hospital because of a fall since when he has been limping with the left leg. X-ray examination revealed no fracture in the hip region, but marked flexor spasm of the thigh persists.

EXAMINATION on October 20, 1937, at the age of two years and ten months,

FIG. 6.—Ring-like shadows of increased density present at the ends of metacarpals and phalanges. Evidence of an old fracture of the right ulna.

revealed the following : Height, 31 inches. Weight, 23 lb. Circumference of head, 20½ inches. Intermeatal measurement (over head), 13½ inches. Face somewhat flattened. Bossing of frontal and posterior parietal regions. Horizontal ridge in fronto-parietal regions. Marked projection in occipital region with hollowing beneath. Anterior fontanelle still admits a finger-tip. Chest narrow (pigeon type) with indrawing of lower ribs on inspiration. No beading of ribs. No disproportion between limbs and trunk. Considerable clubbing of ends of long bones. Only two upper incisors present and these are defective. Finger nails normal. Pupils dilated, regular, react poorly to light. Marked lateral nystagmus. Bilateral primary optic atrophy present. There is no obvious palsy of cranial nerves.

RADIOGRAPHIC REPORT : Typical case of osteopetrosis with extensive changes in the whole skeleton. Evidence of three fractures, one in right fibula, the other in right clavicle and third in right ulna.

OTHER INVESTIGATIONS : Wassermann reaction, negative. Serum calcium, 9·7 mgm. per cent. Inorganic blood phosphorus, 2·7 mgm. per cent. Blood phosphatase, 9·5 units (normal 3·5–8). Blood urea, 21 mgm. per cent. Blood count : Hb, 60 per cent. ; R.B.C., 3,440,000 per c.mm. ; W.B.C., 11,200 ; polymorphs, 38 per cent. ; lymphocytes, 59 per cent. ; hyalines, 3 per cent. ; anisocytosis and poikilocytosis.

He was re-examined recently, shortly after his third birthday, and the condition is still appreciably the same.

Etiology

The numerous theories about the cause of the disease include suggestions of polyglandular dyscrasia—especially a disturbance of parathyroid function—of poisoning with phosphorus or fluorine and of chronic bone infection. Many authors (Nadolny, 1924 ; Llado, 1931 ; Kopylow and Runowa, 1929) conclude that the disturbance is one of calcium metabolism, but the evidence incriminating the parathyroid for this (Péhu, 1931 ; Ellis, 1934) is not at all clear. There remain the undisputed facts of the frequency with which parental consanguinity has been noted in osteopetrosis and the tendency for familial incidence in this disease. Many authors comment also on the large number of miscarriages preceding or following the birth of an affected individual and on the high mortality rate among the sibs.

It is interesting to note that both parents of Kudrjawtzewa's (1930) patients had been married before and that the father had three normal children by the first marriage and the mother one. By their consanguineous union they had five children, two of whom died in infancy and three had typical osteopetrosis. D'Istria (1928) noted a similar occurrence, the father having had three normal children by his first marriage, whereas his union with a first cousin resulted in five children, three of whom died in infancy, one was mentally defective and one had osteopetrosis. Up to date there appear to be recorded 112 cases (including that here described) and in those consanguinity was noted in twenty-three instances. Of the fourteen marriages covering these twenty-three cases eight (ten cases) were between first cousins. Consanguinity was specifically denied in twenty patients (eleven families) and no record was made in sixty-nine instances (forty-nine families). The above points taken in conjunction with the early lethal outcome of the disease lead to the conclusion that osteopetrosis is an inherited recessive defect.

Against this are the records of seven families embracing twenty-six affected individuals in whom the disease was handed down directly from generation to generation. In six instances (Ghormley, 1922 ; Lautenburg, 1926 ; Pirie, 1930 ; Zaleski, 1932 ; Pagenstecher, 1935 ; and Harnapp, 1937) two generations were affected and in one (McPeak, 1936) mention is made of a woman aged seventy, her two daughters, and five grandchildren who were involved. It is unlikely that inbreeding would wholly explain this occurrence, because the disease is so rare, and it is safer to assume that there is also a type of osteopetrosis which is handed down as a simple dominant. Deducting the above twenty-six cases from the total of 112 leaves eighty-six, 11·7 per cent. of which were born to first cousins. The 10 per cent. incidence of first-cousin marriages would probably be greater had the majority of authors made a statement about

consanguinity, but in any case it is significant because the normal rate in the general population is estimated to lie between 0·5 and 1 per cent.

The segregation of osteopetrosis into recessive and dominant would coincide with the suggestion of Harnapp (1937) and McPeak (1936), who divide the cases into the more or less severe or ' malignant ' and the relatively mild or ' benign,' and would be parallel to a condition known as epidermolysis bullosa dystrophica, the severe form of which is a homozygous recessive and the less severe a heterozygous dominant. It is certainly more than a coincidence that all the cases in which direct inheritance can be traced fall into the benign group and that the evidence of consanguinity occurs only in the first or malignant group.

Osteopetrosis is pre-eminently a disease of childhood and early adolescence. It has been diagnosed as early as in utero (Pirie, 1930) and as late as at the age of seventy (McPeak, 1936). Of the 112 cases eighty-one were under and twenty-nine over twenty-one years of age ; in two the age was not mentioned. Sex plays no obvious rôle, because of the 110 instances in which it was stated fifty-eight were male and fifty-two female. No special tendency could be traced in the sibships for those affected to be of one sex and those unaffected to be of the other. Race does not appear to be a factor, because cases have been recorded in many countries, including one in a negro in U.S.A. and another in a Japanese.

Pathology

The essential feature of the disease is the great increase in thickness and density of the cortical and spongy portions of the skeleton and a variable degree of decrease in the space occupied by the bone marrow. Most authors assume that this encroachment of bone on the medullary cavity is responsible for the myelophthysic type of anaemia met with in the severe type of osteopetrosis. The occasional changes in the peripheral blood resembling leukaemia, and the more rare attempts at vicarious haemopoiesis in enlarged liver, spleen and lymph glands are taken to be natural consequences of the same process. It is tempting to explain the anaemia on this simple quantitative basis, but it is equally possible that the changes in the blood-forming elements are primary and that the excessive deposition of bone is a replacement phenomenon. If it is agreed that the condition is an inherited dyscrasia of the mesenchymal tissues responsible for the formation of both the bone and the marrow it can be accepted that the two processes may go on side by side without influencing each other unduly. In favour of this supposition is the fact that great increase in density of bones has often been observed, particularly in those who inherited the disease as a dominant, together with slight or even no anaemia. On the occasions on which the bone marrow was examined (Assmann, 1907 ; Schmidt, 1907 ; Goodall, 1912) it was found to be healthy, although in parts it may be replaced by fibrous tissue. The sclerosing process usually begins near the epiphyseal lines, and opinions differ as to which bones are first affected. In flat bones like the ileum concentric arcs of dense material represent the initial stage, whereas in small bones of hands and feet early condensation produces a ring-like appearance. In long bones there is a tendency for the sclerosis to occur in bands at right angles to their long axis. These bands alternating with the less dense portions give a striped appearance on cross-section. Both the

cortex and the individual trabeculae of the medulla are reported to be thickened and extra bone may also be deposited in longitudinal ridges beneath the periosteum, thus producing a fluted contour. The ends of the long bones are frequently clubbed.

The departure from normal in the affected portions of bones is due, according to most authors who made a study of it (Pirie, 1930 ; Nadolny, 1924 ; Alter, 1931 ; Laubmann, 1934), to a disturbance in endochondral formation of bone which allows the cartilagenous basis to persist. In the skull the distinction between the cortex and diploe is obliterated, the basal bones are greatly thickened and the posterior clinoid processes often clubbed. The meninges may be thickened and on occasions pachymeningitis interna hæmorrhagica has been observed (Kraus and Walter, 1925 ; Lorey and Rye, 1923). Hydrocephalus is common and is possibly explained by the obstruction to venous return through the narrowed foramina at the base of the skull. The bones may show evidence of many fractures, particularly in the ' malignant ' type of disease. Most of these fractures are pathological, and it is not certain whether they are liable to occur through the dense or relatively rarefied areas.

Pirie (1930) stated that the dense portions of the skeleton are soft and friable, but he stands alone in this respect, because the consensus of other opinion (Clairmont and Schintz, 1924 ; Alexander, 1923 ; Lautenburg, 1928 ; Parkinson, 1928 ; and Harnapp, 1937) is that the sclerosed bone is abnormally hard. Nearly all chemical analyses of affected bones gave results within normal limits (Pirie, 1930 ; Kopylow, 1929 ; Kudrjawtzewa, 1930 ; Péhu, Policard and Dufort, 1931 ; and Lautenburg, 1928).

Clinical features

The condition of osteopetrosis is most commonly discovered accidentally when the patients are brought up on account of fractures, apparent rickets, necrosis of jaw bones, severe anaemia or failing sight. This and the ensuing description applies to the severe or ' malignant ' type, which, it is suggested, is inherited in the form of an autosomal recessive defect. Retardation in growth is common and is more marked in those cases in which the disease is fully established early in life. On account of the frequent combination of hydrocephalus and marked bossing of the skull bones the head assumes a characteristic appearance. The veins on the scalp are dilated. The closing of the anterior fontanelle is usually much delayed. The teeth are often late in erupting, defective in quality and decay early. Dental caries combined with compression of nutrient foramina of the jaw bones may result in necrosis of the mandible. Fractures, usually provoked by trivial violence, are common and many of them, by escaping notice at the time, lead to deformities. Callus formation and healing of bones appears to be normal. The encroachment on the foramina at the base of the skull produces optic atrophy which shows itself clinically in defective vision, nystagmus and eventually blindness. Occasionally other cranial nerves are similarly affected leading to lower motor neuron lesions. In younger patients enlargement of lymph glands, spleen and

liver may be found. Despite the disabilities, such as poor vision and anaemia, intelligence is not appreciably impaired.

In the ' benign ' form of osteopetrosis the general condition of the patient is usually not affected and fractures are relatively rare. Here recognition is always accidental, usually when the patients are X-rayed because of trauma.

X-ray appearances are characteristic and apply to both types of the disease. There are symmetrically arranged areas in both the cartilage and membrane bones where dense, rather fuzzy-looking bone appears to encroach and obliterate the medullary cavity. The base of the skull, the long bones and bodies of vertebrae are most prominently involved. The long bones may show alternating transverse bands of more and less opaque areas and clubbing at the ends, corresponding to the pathological findings. As a rule centres of ossification appear at normal times and fusion of epiphyses and shafts are not delayed.

Blood picture.—In the ' benign ' osteopetrosis this is usually normal. In nearly all other cases there is anaemia, most frequently of the hypochromic kind. Immature red cells such as normoblasts or rarely megaloblasts may be present in the peripheral circulation. In infants the blood often shows an increase in white cells, some of which may be immature, but in adolescents and adults this is rare. There are recorded instances in which the disturbance in the blood picture was more severe than radiological appearance of the bones would suggest, but the opposite is even more common.

Chemical analysis of the blood.—Normal values were found in nearly every instance in which the serum calcium and phosphorus were analysed. Notable exceptions were the patient of Schultze (1921) who showed extensive calcification of soft tissues with a blood calcium ' double its normal value ' and the one of Flood (1929) whose serum calcium ranged from 14·6 to 16·6 mgm. per 100 c.c.

Diagnosis

The complete picture of osteopetrosis, especially in its severe form, is so characteristic that it can hardly be confused with any other condition. The x-ray appearance of the skeleton is, of course, the most striking feature, and this is found in both types of the disease. In the differential diagnosis of ' malignant ' osteopetrosis the elimination of leukaemia may prove a difficulty on account of some resemblance in the blood pictures, but in leukaemia the occasional involvement of the bones is more in the nature of invasion and destruction rather than of the excessive deposition of bone as in osteosclerosis. The presence of nucleated red cells in the peripheral blood may suggest Cooley's erythroblastic anaemia, but the x-ray appearances of the bones, especially those of the skull, are entirely different. Increase in density of single bones has been described under the titles of ' ivory vertebra ' and eburnising osteitis, but besides this there is no other point of resemblance to osteopetrosis. Melorheostosis (Léri) is another condition in which there is only a localized increased density of one or more bones of an extremity. Secondary deposits of malignant disease, quite apart from the different age incidence, give an entirely different

x-ray picture. The history would help to eliminate chronic lead, phosphorus or fluorine poisoning which sometimes gives rise to diffuse bone changes. Paget's disease, though bearing some superficial radiological resemblance, has again a different age incidence and a characteristic distribution of bony changes. Pathological fractures may occur in fragilitas osseum, but here there is usually a decrease and never an increase in density of bones.

Prognosis

The ' benign ' form may show a slight increase in tendency to fractures, but apart from that it does not appear to shorten or otherwise appreciably affect the life of the individual. The ' malignant ' form is usually fatal early in life either from anaemia or intercurrent infection. The earlier the disease is fully established the worse the prognosis. Some of the less severe cases may drag out a rather subnormal existence well past adolescence.

Treatment

In the light of present knowledge this can only be symptomatic. Correction of deformities due to fractures may be required, osteomyelitis when it occurs will have to be dealt with, and in a desperate case blood transfusion may stave off the inevitable end.

Summary and conclusions

(1) The condition of osteopetrosis is briefly reviewed.

(2) The hereditary aspect of the disease is stressed and evidence brought forward in support of dividing it into two forms, the benign, which is inherited as a dominant, and the malignant, which is handed down as a recessive.

(3) A personally observed patient is described and a list of cases not included in previous reviews is appended.

Thanks are due to Dr. E. A. Cockayne for his helpful criticism of the section dealing with the etiology.

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APPENDIX

YEAR	AUTHOR	AGE YEARS	SEX	BLOOD RELATIONSHIP OF PARENTS
1931	Wakeley	8	M	No record.
1934	Ellis	$2\frac{10}{12}$	M	Present.
	,,	$1\frac{6}{12}$	M	,,
1934	Shallow, Davis and Farrell	16	F	Absent.
1935	Pounders	$3\frac{1}{2}$	M	No record.
1935	Root	$\frac{6}{52}$	F	Present.
1935	Assmann	25	M	No record.
1935	Parenti	61	M	,,
1936	Spéder	44	M	,,
1936	Kretznar and Roberts	21	F	Present.
1936	Kerr	20	M	No record.
1936	Heidger	'Adult'	M	,,
1936	Stenström	55	M	,,
1936	Wortis	9	M	,,
1936	McPeak	70	F	,,
	,,	42	F	,,
	,,	15	M	,,
	,,	13	F	,,
	,,	6	M	,,
	,,	3	F	,,
	,,	$\frac{11}{12}$	F	,,

THE COOLEY SYNDROME IN AN ENGLISH CHILD

BY

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Cooley's erythroblastic anaemia has been reported in England before (Moncrieff and Whitby, 1934), but, with the two doubtful exceptions of a girl aged nineteen with a negative calcium balance, a marrow showing changes as in osteitis fibrosa and normal erythrocyte variability, mentioned by Vaughan (1936) and an infant with an English father 'of Southern European type' (Bush, 1937), only in children of Mediterranean stock. The only other two children of non-Mediterranean descent in the literature were one described respectively by Cooley (case IV) in his original paper (1927) (she and her father also had positive Wassermann reactions and she was subsequently omitted from the series) and by Grinnan, 1935 (case VIII), a boy of Anglo-Irish parentage, aged nine.

Clinical Record

Olive F., aged ten, is the fourth of five healthy children ranging from nine to eighteen years of age. Her father had influenza in Genoa during the War and again with appendicitis in 1934. He denies having had malaria or venereal disease and on routine examination appears healthy. His serum gave negative results for the Wassermann and Sigma reactions and his serum bilirubin was within normal limits. The only death among his four siblings and eight nieces and nephews was a sister who 'faded out' aged four months. The paternal grandfather was a healthy Sussex man and the grandmother claimed some German blood on her mother's side. The mother is one of a healthy family of eight, has had no miscarriages and is of English descent on both sides. She has never been abroad and has had no illnesses of note. Her serum showed a negative Wassermann reaction, normal fragility and normal bilirubin.

The patient has always been pale. In 1932 at the age of five she was jaundiced and had an enlarged spleen and liver, with a negative Wassermann reaction and hypochlorhydria. The blood showed then an anaemia of 40 per cent. Hb. (Dare); R.B.C., 3·9 million per c. mm.; normal white count; bilirubin, 1–4 units; fragility, 0·4–0·3 per cent.; reticulocytes, 5–7 per cent.; and occasional nucleated red cells. No change in the blood picture occurred

in spite of intensive liver, iron and stomach therapy (see fig. 1). In June, 1935, at the age of eight her spleen and appendix were removed and two transfusions given (Group II—A). The spleen was adherent to liver, stomach and colon. It was enlarged and weighed 200 grammes (normal at this age=80 grammes). Two spleniculi were also removed, one of which on section (figs. 2*a* and 2*b*) showed marked proliferation of endothelial cells, some fibrous tissue hyperplasia especially of the capsule, large ' active ' germ-centres to the Malpighian bodies, and little or no endarteritis, but some increased perivascular fibrous tissue. The pulp spaces were much reduced ; there were no islands of myeloid or erythropoietic tissue to be seen in the section except a small area at one

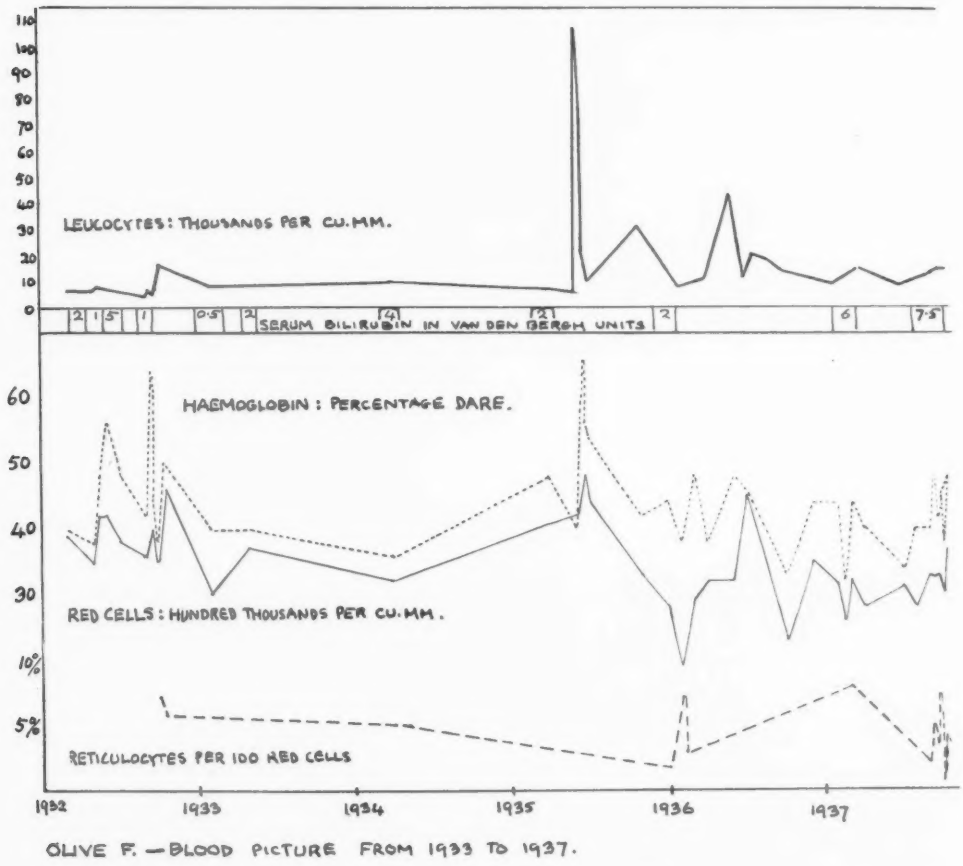

FIG. 1.—Chart of blood changes.

point under the capsule. No parasites were to be seen, no foam cells, no pigment, no sickling of the red corpuscles and few nucleated forms in the blood spaces.

These drastic measures temporarily raised her haemoglobin to 66 per cent. (Dare), but the red cell count remained stationary and the platelets normal. Splenectomy was followed by an empyema, which raised the white cells to 107,000 per c. mm. The empyema was drained with rib-resection. Two months after splenectomy, the fragility of her corpuscles was recorded as 0·4–0·3 per cent. (normal).

A year later her joints began to swell and an abscess in the chest wall was opened. Her blood showed a white count of 43,200 per c. mm., with 76 per

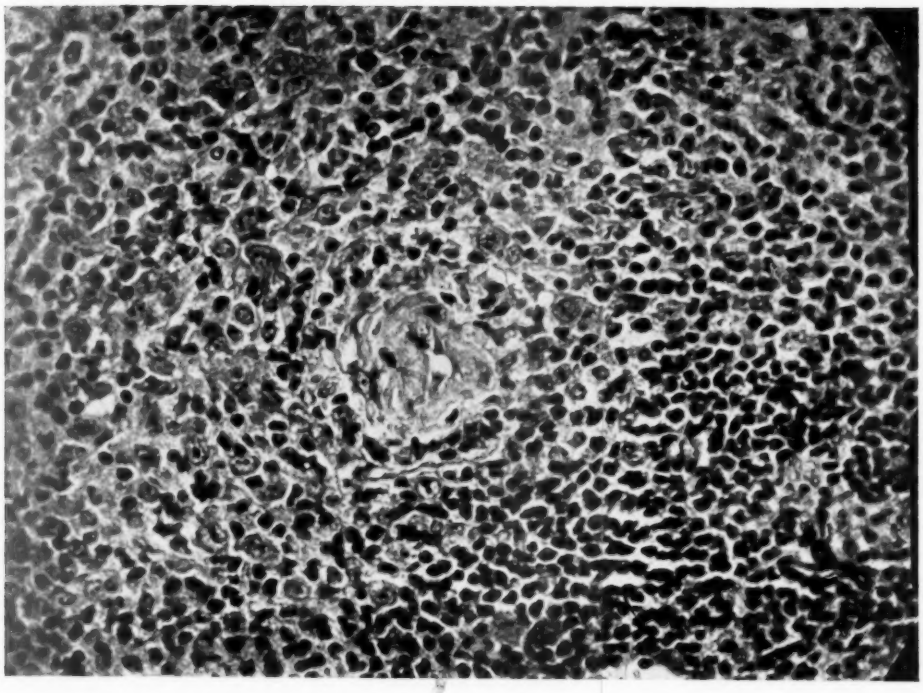

FIG. 2*b*.—Photograph of spleen section. High power.

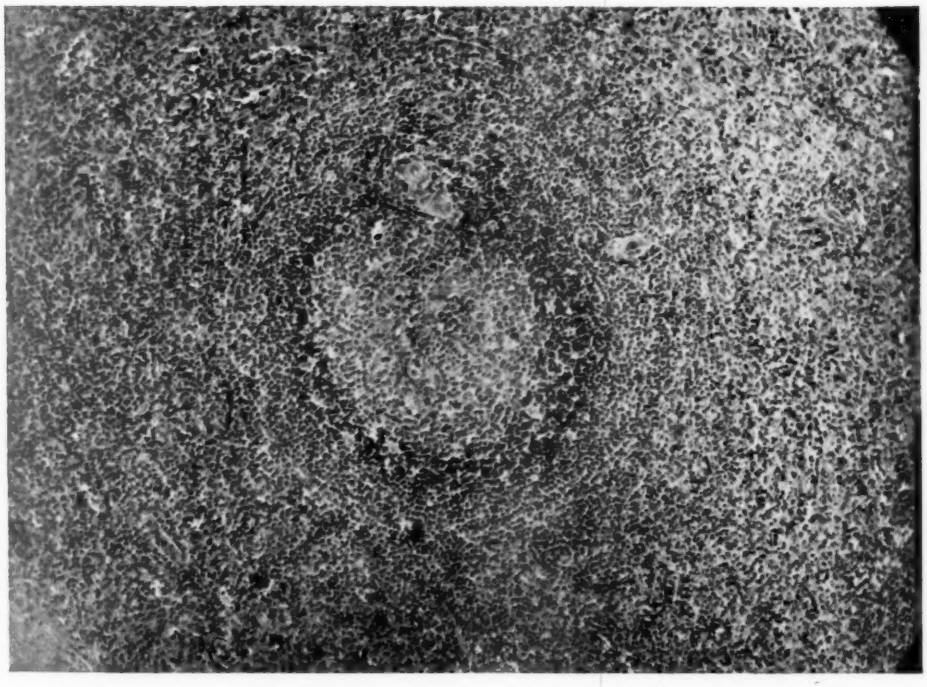

FIG. 2*a*.—Photograph of spleen section. Low power.

cent. polymorphonuclears, 2 per cent. myelocytes and numerous nucleated red cells. She has often shown a low-grade pyrexia.

PHYSICAL EXAMINATION : AUGUST 26, 1937.—The patient was a pale, intelligent girl weighing 53 lb. 6 oz. and of a muddy-yellow and freckled complexion. The photograph (fig. 3) shows a rather wide face across the cheek, which, although not mongoloid, is suggestive. No abnormality was found except the abdominal and thoracic scars, a liver about three fingers' breadths below the costal margin and a systolic murmur at the heart apex, which was

FIG. 3.—Photograph of patient, 1937.

displaced outwards. A teleradiogram of the heart (at 6 feet) showed a diameter of 11½ cm., with enlargement of both ventricles. In particular the tongue and teeth were normal, as also was the chest. There was no evidence of joint disease or rickets and the lymph glands were not enlarged. An electrocardiogram shows slight left axis deviation.

The mean corpuscular volume by Wintrobe's method (1933), using his oxalated tube (Wintrobe and Landsberg, 1935), was 75 cu.μ, mean corpuscular haemoglobin 23$\gamma\gamma$, mean corpuscular haemoglobin concentration 17 per cent. A Price-Jones curve (see fig. 4) from a film taken at the same time (July 24, 1937), measured by the method of Hynes and Martin (1936), showed a mean diameter of 8·32μ, a coefficient of variation 13 per cent., standard deviation 1·08, macrocytosis 40 per cent., microcytosis 2 per cent. The mean corpuscular thickness was thus 1·39μ, the diameter/thickness ratio 6 : 1, and the volume/thickness ratio 54 : 1. Fresh blood showed no sickling in a sealed preparation from which air was excluded for two hours at 37° C. There were many poikilocytes present and much crenation. Platelets numbered 192,000 per c. mm.

The stained film showed 14 per cent. of target forms in 1,000 red cells (Barratt, 1937). No parasites were seen either normally or by the thick film

technique. Staining defects were seen in a variable proportion of the red cells—small, unstained areas, often oval or round, in the centre or periphery of the corpuscle, sometimes one, usually more than one in the cell. There was no obvious association with large or small, stippled, polychromatic or target forms. The defects were best seen by green light in films counterstained with eosin, when the centre of the defect often appeared to be filled up, producing a ' ring ' appearance (see figs. 5*a* and 5*b*). The edges of the defects were

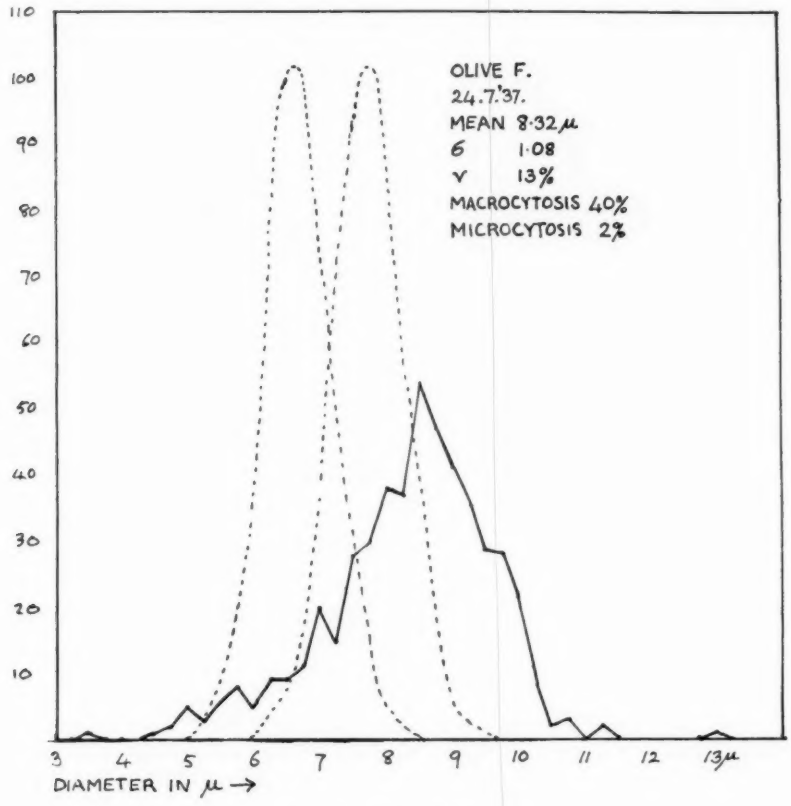

FIG. 4.—Price-Jones curve.

usually sharp, and, although no illustrations have yet appeared of these defects, they correspond with the description (' an uneven distribution of haemoglobin ') given first by Cooley and Lee in 1932. The resistance to hypotonic saline was increased and the span widened (fig. 6).

The Wassermann reaction was negative in 1932 and again in 1937, both before and six days after a fever-provoking dose of sulpharsphenamine. The Sigma reaction was also negative. The Mantoux test gave a negative result at a dilution of 1/1000.

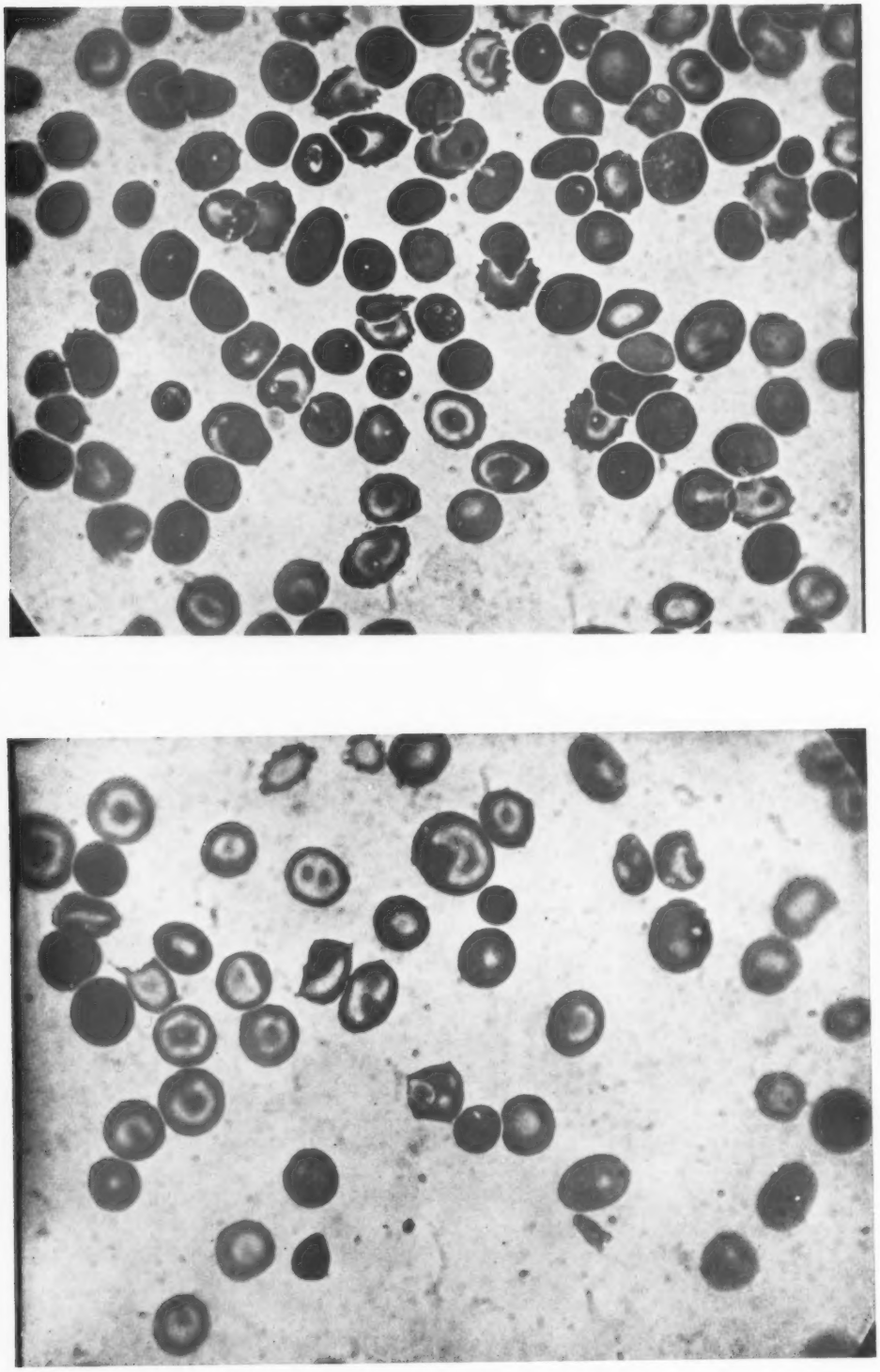

FIG. 5 (*a* and *b*).—Photograph of blood showing target cells, haemoglobin defects and normoblasts.

BLOOD COUNT SHOWS:	24.7.37	20.8.37	1.9.37
R.B.C. mill. per c. mm.	3·1	2·8	3·3
W.B.C. thous. per c. mm.	8·5	10·4	17·0
Hb. grammes per cent.	5·4	6·4	6·4
Polymorphonuclears, per cent.	35	35	37
Lymphocytes ,,	55	50	56
Monocytes ,,	4	7	3
Eosinophils ,,	2	7	4
Mast cells ,,	0	0	0
Myelocytes ,,	4	1	0
*Early erythroblasts (per 100 white cells)	1	1	1
Late erythroblasts ,, ,,	6	6	7
Normoblasts ,, ,,	600	540	640
Reticulocytes per 100 R.B.C.	Not enumerated	3·0	2·2
Polychromasia	++	+	(+)
Cabot's rings and Howell-Jolly bodies	+++	(+)	−
Stippling	+++	+	+

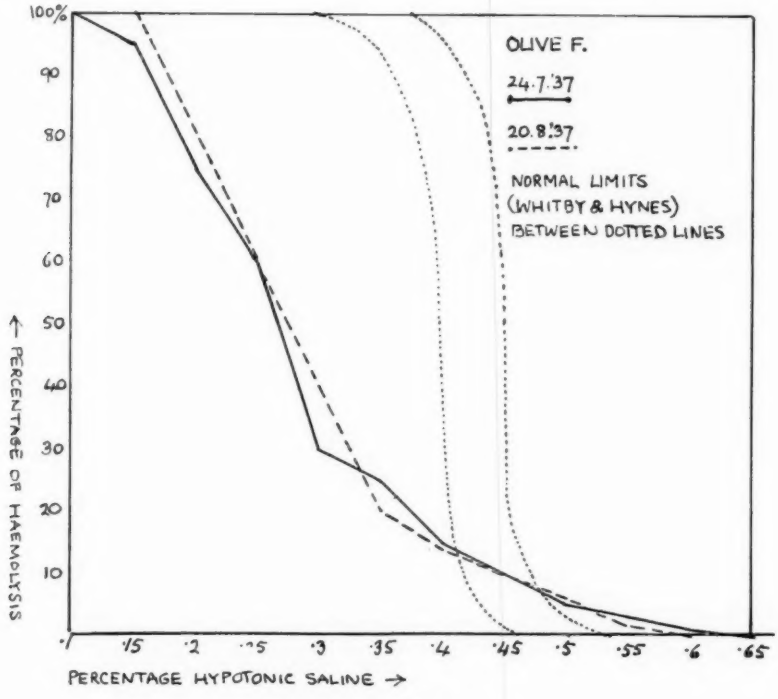

FIG. 6.—Fragility curve.

BIOCHEMICAL INVESTIGATIONS.—The van den Bergh indirect method showed $2\frac{1}{2}$ units of bilirubin ; the faecal fat was within normal limits ; a fractional test meal showed free acid absent (September 1, 1937), and, a week later, free acid present in two out of seven specimens at two and two and a half hours.

* Nomenclature of Kato and Downey, 1933.

FIG. 7.—Skiagram of skull (antero-posterior), outlined outer surface.

The urine showed a weakly positive reaction for urobilin and the faeces a strongly positive reaction.

SKELETAL CHANGES.—The skull is enlarged. In the antero-posterior view (fig. 7), the parietal eminences are 1–1·2 cm. thick (teleradiogram). The outer table has almost disappeared, but the general density is increased. No spiculation is seen. In the lateral view, the characteristic thickening of the frontal

FIG. 8.—Skiagram of skull (lateral).

and occipital regions is seen (fig. 8). The clavicle shows rarefaction and a coarse trabeculation—changes that are seen also in the metacarpals and metatarsals. The characteristic increase in width is not seen except, slightly, in the fifth (fig. 9). The ribs show no evidence of rickets, but there is a fusiform thickening in the region of each tubercle (cf. Whipple and Bradford, 1936). The femur, tibia, radius and ulna show no abnormality except lines of bony arrest.

TREATMENT.—The patient has been given liver extract, hog's stomach and iron for five years. For three weeks (beginning September 4, 1937) quinine and ethyl carbonate 7½ grains thrice daily were given after an initial test dose of 5 grains with no effect on haemoglobin, red cells or reticulocytes. Mercury ointment (60 grains) was then rubbed into the skin daily for a week from September 25, 1937, and potassium iodide given for two days until an iodide rash appeared. On September 29, 1937, sulpharsphenamine (0·015 gramme) was given intramuscularly with novocaine. This was followed two days later by malaise and fever (up to 102° F.), which persisted for a week. Six days after the injection with the temperature still raised, her serum was found, as before, to be Wassermann negative. It was thought inadvisable to continue

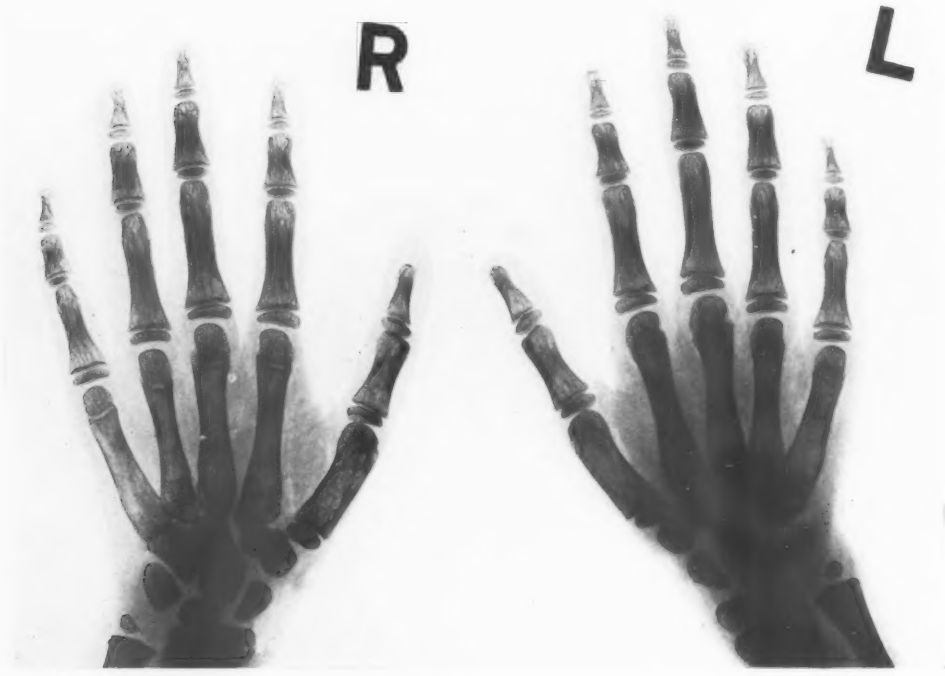

FIG. 9.—Skiagram of hands.

this line of treatment, and, since October 7, 1937, the child has been having iron and ammonium citrate 20 grains three times a day and anahaemin 2 c.c. intramuscularly weekly. Her blood picture is now as it has been always. Spray X-ray therapy (Hunter, 1936) has not been tried.

Differential diagnosis

The following must be considered :

A. Congenital syphilis.—The absence of other clinical evidence in the child and total absence in the parents, negative Wassermann reactions, especially after a provocative dose of sulpharsenobenzol and mercury, and the negative Wassermann reaction in mother and father would seem to exclude

this. The staining defects in the red cells also were not seen in the original case IV of Cooley and Lee (1932) with congenital syphilis.

B. Congenital or neonatal malaria.—This is unlikely in England. Nittis and Spiliopoulos (1937) from Greece have recently reported success with anti-malarial treatment in children who presented the Cooley syndrome, but which were indistinguishable, except for the absence of parasites, from congenital malaria. Spyropoulos (1936) also from Greece cites twelve infants and children showing secondary or symptomatic Von Jaksch' syndrome with liver and spleen enlargement, normoblastosis, anaemia and leucocytosis, some with mongoloid features (no skiagrams) due to such diseases as malaria (two cases), leishmaniasis (three cases), chronic tonsillar infection, toxic-infectious hepatitis, 'alimentary' anaemia, and 'geophagic' anaemia with nematodes; all cured by specific methods. In the child described here the failure of adequate quinine therapy and the absence of parasites from her father, who had been to Italy before the child's birth, but denies having had malaria, and from the child, examined by thick and thin film methods, would seem to exclude malaria.

C. Other infectious agents, such as leishmania : there was no evidence of these.

D. Sickle-celled anaemia : this is unlikely in a white child with no possibility of negro admixture, although it has been reported from America in a Greek (Cooley and Lee, 1929), Italians (Rosenfeld and Pincus, 1932), temporarily in a syphilitic and malarial American of Scotch-Irish ancestry (Sights and Simon, 1931), and in Mexicans (Wallace and Killingsworth, 1935). Against this is the absence of sickling in fresh blood, the absence of the peri-Malpighian 'pool of blood' described by Rich (1928) as characteristic, and the absence of sickling in the formalin-fixed spleen (Bennett, 1929). The clinical history is not that of typical sickle-celled anaemia, although joint symptoms occurred once (cf. Josephs, 1928).

E. Acholuric jaundice is excluded by the decreased fragility and absence of response to splenectomy.

F. Bone diseases such as myelomatosis, Albers-Schönberg disease, carcinomatosis, myelosclerosis, Hodgkin's disease can be excluded by length of history and absence of radiological evidence.

G. Nutritional anaemia and coeliac disease are excluded by lack of response to liver and by the normal faecal fat.

Discussion

This disease, of which Whitby and Britton (1937) give most of the important bibliography up to 1937, first described by Cooley and his associates (1925) is now believed by this author and by Whipple and Bradford (1936) to be a congenital and familial disorder of metabolism. All the children previously described, with the three possible exceptions mentioned above, and there are now more than sixty cases reported, have come of Mediterranean stock : Spanish (Sendrail, Lyon and Lasserre, 1936), Italian, Greek, mulatto and Syrian ; they have come sometimes from the same village and have been reported in twins and often in families, especially if the parents were related.

The diagnosis must, therefore, be open to considerable suspicion in a child with a blue-eyed English policeman as father, an English mother and four healthy siblings.

These points favour the diagnosis :

1. The long history of absence of response to treatment (cf. Whipple and Bradford, 1936).

2. The cardiac enlargement and slight left axis deviation (Nemet and Gross, 1936 ; Caffey, 1937).

3. The diameter-thickness ratio. The average cell is abnormally flat ; its volume is on the low side of normal, and the mean haemoglobin content and concentration are both low (as noted by Bradford and Dye, 1936), but the cell thickness is markedly decreased, being 1·39μ as compared with a normal range of 1·7–2·5μ. The diameter-thickness ratio is thus raised above the upper normal limit of 4·2 : 1 and the volume-thickness ratio above the normal 42 : 1. The diameter-thickness ratio is usually normal, it is interesting to note, in pathological conditions, except in acholuric jaundice, when it is decreased, and in some cases of erythroblastic anaemia with idiopathic steatorrhoea, leukoerythroblastic anaemia with myelosclerosis, and cirrhosis of the liver, when it is increased. (Flat cells are not, however, diagnostic of these conditions, as in some other cases a normal ratio was found (Vaughan and Goddard, 1934).) Also, relative flattening occurs in obstructive jaundice, with an increased diameter and increased ratios (diameter/thickness=5 : 1, volume/thickness= 55 : 1). This lack of spherocytosis is intimately associated with an increased resistance to hypotonic saline (Haden, 1934) (see below).

4. The resistance to hypotonic saline : this and the large number of target cells in the stained film may possibly in this case be due to splenectomy, since it is said (Whitby and Hynes, 1935) that both the resistance (due to an increase in critical volume, Gordon, Kleinberg and Ponder, 1937) and the target cells are increased after this operation. I have examined, however, through the courtesy of Dr. Whitby, a film of blood from his patient (Moncrieff and Whitby, 1934), and although no splenectomy was performed, there are target cells present, and these authors noted a slightly increased resistance to saline. Many authors note decreased fragility (especially Baty, Blackfan and Diamond, 1932 ; Daland and Worthley, 1935 ; Frontali, 1937) and some have found a slightly increased fragility as well, although Cooley and Lee (1932), while observing that haemolysis was sometimes incomplete even in distilled water, denied that a prolonged span occurred. It is difficult to correlate the recorded figures, as they have used almost entirely the qualitative and not the quantitative technique. It appears, however, that even in patients that have not been subjected to splenectomy, the span and the resistance are both increased. Since Whitby and Hynes (1935) have shown that the similar increase in resistance in infants is not due, as has been suggested, to the high reticulocyte count, it seems probable that the similar increase here is due not to the immaturity of the red cells, although the nucleated cells behave like leucocytes in such solutions as dilute acetic acid, but to the abnormal shape of the corpuscles eventually formed (see Castle and Daland, 1937).

5. The Price-Jones curve shows a typical spread, noted in 1934 by Moncrieff and Whitby and in 1936 by Bradford and Dye, with greatly increased standard deviation and coefficient of variation. The latter authors also noted a marked increase in diameter and macrocytosis with a still further increased standard deviation and macrocytosis after splenectomy.

6. The staining defects in the red cells. Since the original observation of these in 1932, although many papers have been published only four mention the defects, three citing Cooley without corroborating him (Kelly and Hill, 1935 ; Yaguda, 1935 ; and Grinnan, 1935), and the other confirming the ' mottled appearance with irregular clumping ' (Kato and Downey, 1933). It must be noted that Hitzrot (1928) described an irregular staining of the red cells in this disease. According to Cooley and Lee (1932), a similar but very much less marked irregularity occurs in sickle-celled anaemia, where the cell is smaller and the reticulocytes higher. These defects are present in films from Moncrieff's patient and from other children with typical Cooley's anaemia, which, by the courtesy of Dr. Diamond and Miss Daland of Boston, Massachusetts, I have been enabled to see. They become especially numerous after splenectomy and similar to those in the present case. A few poorly marked defects were seen also in sickle-celled anaemia and in a small proportion after splenectomy for other conditions. They are not present in films from patients with typical acholuric jaundice, leukaemia, pernicious or nutritional anaemia or carcinomatosis with leukoerythroblastic anaemia.

7. The skeletal changes : the picture in general corresponds to a late and sclerotic change (see especially Caffey, 1937). The typical spiculation is not present. This, however, is not a necessity in the diagnosis, as in some cases observed for as long as six years (Caffey) it is never seen (Wollstein and Kriedel, 1930 ; Crawford and Williamson, 1933 ; Hitzrot, 1928) and in other anaemias it is sometimes present : acholuric jaundice (Friedman, 1928 ; Snelling and Brown, 1936), sickle-celled anaemia (Vogt and Diamond, 1930 ; Moore, 1929 ; Le Wald, 1932 ; Rose, 1929 ; Levy and Schnabel, 1932) and erythroblastic anaemia of Gee-Thaysen disease (Bennett, Hunter and Vaughan, 1932)).

8. The spleen : this presents a variable picture as described in the literature. It is impossible to describe anything as typical, although there is generally fibrosis, sometimes erythroblastic activity, and occasionally reticulo-endothelial proliferation. In this case it is unlike the only other spleen section from a case of Cooley's anaemia that I have seen (Moncrieff and Whitby, 1934), which showed wide pulp spaces, but it corresponds closely with a description by Capper, 1931, Case II.

9. The response to splenectomy, of which the only obvious effect was to increase the nucleated red cells in the blood. This phenomenon occurs constantly in the disease, and the rise is often startling, e.g. from 100 to 7000 per c. mm. (Fries, Duhan and Shair, 1933). In other diseases splenectomy does not produce such an effect (Wollstein and Kriedel, 1930). In this patient there are no definite figures, but ' occasional ' become ' numerous ' nucleated red cells after splenectomy, until to-day when they number between 50,000 and 100,000 per c. mm. While the opinion has been held that splenectomy may

retard the progress of the disease (e.g. Cooley,1932), the majority of observers now believe that neither this nor any other treatment except general hygienic measures and the prevention of deficiency anaemia has any effect on its usually prolonged and ultimately fatal course. (See especially Whipple and Bradford, 1936.)

10. The test-meal findings are similar to those of Racugno (1936), who found, with histamine test meals, traces of free acid in two, no traces in two other cases, and Whipple and Bradford (1932), who found with an alcohol meal no free acid in one case.

Conclusions

This child is suffering from a chronic erythroblastic anaemia indistinguishable from Cooley's anaemia. Whether this label with its prognostic implications should be withheld on ' racial grounds ' is a debatable point. It would seem of more practical use to include this case and other cases of atypical ' haemolytic ' jaundice showing decreased fragility and defects of the erythrocytes, bone changes and a similar response to splenectomy until other differences are discovered. More observations on the red cell staining defects may clarify the situation.

Summary

An anaemia similar to the Cooley type in an English child of ten years is recorded, with observations on staining defects, fragility and size of the red cells.

I am indebted to Dr. J. N. O'Reilly, under whose care the child has been, for permission to publish this record and for his advice and helpful criticisms ; to Dr. W. Smith for some of the pathological examinations, and to Dr. Fane Tierney for the skiagrams.

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CORRECTION

A STANDARD INTRAVENOUS GLUCOSE TOLERANCE TEST

In the paper entitled A Standard Intravenous Glucose Tolerance Test by Dr. T. Crawford, published in the last number of the Archives, the work of Dr. C. Wallace Ross was incorrectly quoted.

It was stated that he had used a watery solution of glucose for an intravenous glucose tolerance test, and the suggestion was made that the watery medium was responsible for some irregular and double-peaked curves which he had reported. Actually Dr. Ross used a solution of glucose in normal saline for the tests, so that the suggestion made cannot be supported.

The author of the paper regrets having allowed this error to arise.

CASE REPORTS

A CASE OF DIABETES MELLITUS IN A YOUNG INFANT

BY

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Diabetes mellitus occurring in the neonatal period has so seldom been reported that the following case seems worthy of record.

The patient was a female child, aged twenty-five days, born of healthy parents, with no family history of diabetes. The mother, aged twenty-four years, had had two previous pregnancies ; in both cases birth was premature. The first child is alive and well, aged two years ; the second died within a few hours of birth.

The third child, the subject of this communication, was also born prematurely, in the twenty-eighth week of pregnancy. This apparently was normal in every respect and labour was easy and spontaneous. At birth the baby seemed healthy, cried immediately, was quite vigorous and sucked well. She is said to have weighed only 3 lb. In spite of apparently adequate breast feeding, the child failed to thrive and became weaker and at one week she was unable to suck and was put on to spoon feeding, at first on breast milk and later on a sweetened, condensed milk. She never took well, however, being unable to swallow more than 2 to 3 teaspoonfuls at each feed. She became extremely weak and emaciated, and at twenty-five days was admitted to hospital, having been vomiting persistently during the two previous days.

On admission, the child was grossly emaciated and dehydrated and weighed only 1·02 kgm. Respiration was shallow, the temperature subnormal, the pulse imperceptible and the heart sounds almost inaudible. She was not deeply comatose as she responded feebly to painful stimuli, but she could not suck and could only swallow with difficulty. The umbilicus was clean, no abnormal physical signs were detected in chest or abdomen and there was no otitis media. A tentative diagnosis was made of prematurity with marked feebleness.

The child was wrapped in cotton-wool and kept under an electric blanket. All disturbance was avoided ; frequent small feeds were given by pipette and these were swallowed with difficulty but retained.

Several hours after admission a specimen of urine was obtained and was found to contain albumin : it gave a strong reduction of Benedict's solution and the phenyl glucosazone test was positive. The blood-sugar was 542 mgm. per cent. The child died shortly after this observation was made and before any attempt could be made to treat the diabetic condition.

Post-mortem examination was carried out by Dr. Guthrie fourteen hours after death. A gross macroscopic hypoplasia of the pancreas was found, the organ weighing only 1·06 gm., whereas normally the pancreas in the new-born child weighs about 3 gm. On microscopic examination a great diminution in the number of islets of Langerhans was found, with no evidence of inflammatory changes in the pancreas. Owing to post-mortem degeneration, it was impossible to get any information about the histo-pathology of the islet tissue. The only other abnormal findings were terminal broncho-pneumonia and mild gastro-enteritis.

Comment

The clinical and post-mortem findings in this case point almost certainly to it being one of true diabetes mellitus. The hypoplasia of the islet tissues observed cannot be attributed to the prematurity, as Nakamura (1924) has shown that the islet tissue normally makes its appearance about the thirteenth week and attains its greatest development by the sixth to seventh month of foetal life.

Discussion

Study of the literature on this subject shows that diabetes in the neonatal period is extremely rare.

Lawrence and McCance (1931) described a case of an infant which developed a spreading gangrene at the age of fourteen days, and four days later was found to have marked glycosuria, with blood-sugar of 600 mgm. per cent. The child recovered, after massive insulin therapy, and four weeks later showed a normal sugar tolerance. They regarded this as a true case of diabetes mellitus, but in view of the rapid and complete recovery, this seems hardly justified. They then reviewed the literature on diabetes in infancy. They stated that they would regard as established, (*a*) cases showing marked diabetic symptoms (thirst, polyuria, wasting) with heavy glycosuria, even if hyperglycaemia was not established, and (*b*) cases showing recurrent hyperglycaemia of over 200 mgm. per cent. even in the absence of diabetic symptoms. They cited seven cases described as diabetes in infants under one month, and accepted only two of these as proven. One of these was a case described in 1852 by Kitselle (his own child), who appeared well at birth but at fifteen days showed thirst, polyuria and glycosuria, and thereafter became emaciated and died at the age of six months. The second was a case described by Ramsay (1926) ; it was a child aged three weeks with glycosuria and marked diabetic symptoms. The child recovered after treatment with insulin and four years later was well and showed normal sugar tolerance.

Lewis and Eisenberg (1935) described a further case. A female child, aged eleven days, with double otitis media and slight bullous impetigo, was found to have a glycosuria and a blood-sugar of 520 mgm. per cent. She died several days later, in spite of insulin treatment. At post-mortem examination a congenital deficiency of the islet tissue of the pancreas was discovered, along with several inflammatory processes (pneumonia, impetigo, and otitis media), nephritis and a congenital cardiac lesion with general passive venous congestion.

Limper and Miller (1935) described a case in an infant of three weeks. This child had developed spreading gangrene of the leg at eleven days and at three weeks was found to have glycosuria with a blood-sugar of 900 mgm. per cent. It was moribund by this time, and in spite of insulin treatment died within a

few hours. At post-mortem examination an acute degenerative lesion of the islet tissue was found, also extensive arterial thrombosis, involving the aorta and many of its branches, which was apparently not due to umbilical sepsis, although this was present.

Of these five cases there can be little doubt that three of them were examples of true diabetes. In the case described by Kitselle (1852) symptoms persisted till death ; in that of Lewis and Eisenberg (1935) there was congenital deficiency of the islet tissue ; while in the case described by Limper and Miller (1935) there was acute degeneration of the islet tissue. The other two cases are not so convincing. That of Lawrence and McCance (1931) recovered completely in four weeks and it may be that the glycosuria was dependent on toxaemia arising from the gangrene of the leg, while the fact that Ramsay's case recovered completely in six weeks and was quite well four years later makes it doubtful if it was a case of true diabetes mellitus. It is interesting to note the similarity of the patient described by Lewis and Eisenberg with the one described in this communication.

The following table summarizes the findings in the above cases :

TABLE 1

CASE	AGE WHEN DETECTED (DAYS)	GLYCO-SURIA	BLOOD-SUGAR, MGM. PER CENT.	FATE	POST MORTEM
Lawrence and McCance (1931).	18	+	600	Recovered	—
Kitselle (1852) ..	15	+	—	Died at 6 months	—
Ramsay (1926) ..	21	+	225	Recovered	—
Lewis and Eisenberg (1935).	11	+	520	Died	Hypoplasia of islet tissue.
Limper and Miller (1935).	3	+	900	Died	Acute degeneration of islet tissue. Arterial thrombosis. Gangrene.
Devine (1937) ..	25	+	542	Died	Hypoplasia of islet tissue.

Summary

A case of diabetes mellitus occurring in a child aged twenty-five days is described. Post-mortem examination revealed marked hypoplasia of the islet tissue of the pancreas. From a review of the literature it appears that only three other unequivocal cases of neonatal diabetes have been reported.

I am indebted to Professor G. B. Fleming for permission to publish this case, and to Professor N. Morris and Dr. F. J. Ford for their assistance and encouragement.

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WILMS' EMBRYOMA

A Clinico-Pathological Study

BY

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The malignant growths variously called ' Wilms ' tumours, adeno-sarcomata, embryomata or nephroblastomata are among the most frequent of those occurring in childhood.

Wilms in 1899 in his valuable monograph was the first to explain the etiology of these tumours on an embryological basis, and by his analysis of fifty-one cases established the group as a definite entity. He was not, however, the first to describe the tumour, for forty-six of the cases to which he referred had been published by others, notably by Birch-Hirschfeld (1898), who reported four cases ; Heineke (1897), who reported nine cases ; Perthes (1896), three cases ; and Ribbert (1892), four cases. All these authors recognized the peculiar ' mixed ' structure of these tumours and called them rhabdo-myosarcoma, adeno-sarcoma, embryonal adeno-sarcoma (Birch-Hirschfeld).

The terminology and the origin of these neoplasms have been much in dispute and the subject of much controversy. Although everyone who has studied them agrees that they are embryonal in that they arise in the region of the developing kidney, there are at least two conflicting views as to their precise origin. It is obvious that the constituent cells of these tumours must be formed either very early or very late in the process of development of the kidney. They cannot arise from the Wolffian body, as this does not take part in the formation of the permanent kidney ; and the frequent presence of immature glomeruli and fully-formed tubules in these tumours indicates that they originate either very early in embryonic life, from a multipotential cell, or at a much later stage, from the metanephros in which the glomeruli and tubules of the permanent kidney develop. The former alternative, expounded in 1899 by Wilms, is the

generally accepted view. Wilms postulated that at an early stage in development of the Wolffian ridge undifferentiated cells are present which can give rise to the cells of the nephrotome, the myotome and the sclerotome. That is to say, they differentiate into cells which form the kidney, muscle, and cartilage. Some of these undifferentiated cells become concentrated at the site of the developing kidney and there give rise later to tumour masses in which may be found muscle fibres and cartilage.

Directly opposed to this view is that of Busse (1899), whose opinion has recently been supported by Nicholson (1931). Busse considered that these tumours arose from the metanephros at a late stage in development and that the more primitive cells found in them resulted from metaplasia. Nicholson, in accepting this view, regarded the presence of glomeruli as evidence of a metanephric origin. His opinion is that in differentiation and co-relation of its several parts this embryonal tumour resembles, and represents, the developing kidney. As, however, it grows without subserving any useful function it is, and remains, a ' tumour ' and is best described as a ' tumour malformation.'

This view cannot explain the presence in these tumours of the muscle fibres which have been reported in a fairly high proportion of cases by various authors. (McCurdy found them in 37 per cent. of his cases.) Another objection to this view is the fact that the tumours are seldom in or incorporated with the kidney. They are nearly always separated from the kidney by a definite fibrous capsule, and although the kidney may be stretched over the tumour, infiltration of the kidney substance is uncommon. If these tumours are to be regarded as part of the developing kidney it would be expected that they should be incorporated in the kidney substance and situated in the interior of that organ. These objections make it difficult to accept this view of their origin.

The nomenclature may be said to be varied if not apt, although the time-honoured custom of attaching the name of a discoverer of, or of an authority on, a disease to that disease has been duly followed by the title of ' Wilms' tumour.' In an attempt to conform with this custom while giving the simplest possible description compatible with known facts it has been decided in the present paper to refer to the tumours as ' Wilms' embryomata.'

Although these tumours are among the commonest of malignant growths in children, there has been only one large series which has been reported from this country, that of McCurdy (1934), who studied thirty-one renal tumours of which twenty-seven were ' nephroblastomata.'

In America, on the contrary, much interest has been shown in them especially from the point of view of prognosis and treatment. Priestley and Broders (1935) reviewed sixty-five cases treated at the Mayo Clinic, of which forty-four were followed up. Only two patients were older than fourteen years of age. Of the forty-four patients traced forty had died. Nephrectomy had been performed in twenty cases and of these fifteen had died. One had survived 13·2 years and one 3·2 years after operation. The other two had been operated on only six months previously. One case was not traced. Not one patient treated by radiation alone had survived. However, of Poule and Ritchie's six cases (1935) the only one still alive (three-and-a-half years after operation) had received x-ray treatment alone.

In 1931 Prather and Crabtree published four of their own cases and reviewed all the cases reported since 1924, a total number of 111 ; 70 per cent. of these proved fatal within fifteen months of the onset ; 12·3 per cent. survived surgery two or more years ; whilst 18·4 per cent. died within one month of operation.

Geschickter and Widenhorn (1934) reported thirty-five cases, thirty of which were under five years of age. One patient was an adult. They followed up twenty-five cases and found not one alive beyond the five-year period. Most of them died or showed metastases within two years.

Wollstein (1927) made a careful clinico-pathological study of seventeen ' embryonal adeno-sarcomata.' One patient survived into adult life and was still alive thirty years after operation. Two others were alive ten months and six-and-a-half years after operation.

Dean and Pack (1932) collected sixteen cases of ' nephroblastomata ' in which the average duration of life after nephrectomy was nine months. One patient survived three years and another two years after the onset of symptoms. No permanent cures occurred.

From these melancholy figures it follows that the prognosis in any individual case appears to be a gloomy one. It is impossible to predict either from the age of the child or the histological appearance of the tumour which child is likely to survive.

Clinical aspects

The series described in this paper consists of twenty-six cases from the post-mortem records and case notes of the years 1921–37 inclusive. One of these (No. 1) is of special interest and is being reported fully by Dr. D. N. Nabarro. We are indebted to him and also to Mr. C. Donald, under whose care the patient was, for their permission to include it in this series for statistical purposes.

In the corresponding period there were only five other tumours primarily renal in origin. Histologically three were sarcomata, one was a carcinoma and the fifth was not identifiable.

In ten of the cases an autopsy was performed (three autopsies in which the sections were not available have not been included). In the remainder the diagnosis was made by examination of the tumour after removal or of material obtained by biopsy. Ten of the patients were males and sixteen females. The age incidence is shown in the following table :

Age in years	0–1	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9
No. of cases	3	5	7	4	4	0	1	1	1

From this it is seen that nearly half of the total number occurred in the second and third years. There were three children of less than one year of age and one was only two months old. Only three tumours were found in children over five years of age.

Presenting symptoms.—In the table below, the presenting symptoms are analysed. It was not always possible to discover what these were, as in some instances the history was very vague.

The commonest mode of onset is, therefore, a progressive enlargement of

the abdomen. It should be mentioned here that in several cases there was, on admission, a considerable degree of abdominal enlargement which had not been noticed by the parents.

Haematuria was an infrequent symptom. As a presenting symptom it occurred in only four cases ; two of these were sent into hospital with a diagnosis of acute nephritis. In a fifth case there was haematuria twice late in the course of the disease. Many writers have emphasized the infrequency of haematuria in this class of tumour. Occasionally, as in Bothe's patient (1931), who had nine attacks of painless haematuria, it is a prominent symptom.

PRESENTING SYMPTOM	NO. OF CASES
Swelling of the abdomen	11
Abdominal pain :	
Generalized	2
Epigastric	3
In the loin	1
Haematuria	4
Wasting, pallor, debility	5

The onset of these neoplasms was, therefore, in most cases insidious and the tumour had usually reached a considerable size before the patient came to the doctor. In seven cases, however, the onset was more acute. In three of these there was sudden onset of haematuria (see table) ; in two others there was a recent history of vomiting with the passage of blood in the stools, and in the remaining two, abdominal pain.

Little information about the blood picture is available in this series. Only six patients had their blood examined. Five were anaemic, three severely. In four the colour index was below unity ; in the other it was 1·1. There were no nucleated red cells in the peripheral circulation in any of the five. There were no significant changes in the leucocyte count.

Pyrexia was not a feature of the clinical course, a fact which contrasts with a recently recorded series of sympathoblastomata (Stern and Newns, 1937). In three patients there were occasional rises of temperature to 101°–102° F. lasting for two to three days, but there was no persistent raising of temperature nor any type of periodic fever.

Results of operation.—In sixteen cases it was possible to remove the tumour. Two patients died within a short time of admission before a nephrectomy could be performed ; in two others no operation was attempted ; and in the remaining six cases the tumour was found to be inoperable, either because it was too large and too adherent or because of secondary deposits.

Of the patients who had nephrectomies one died shortly after the operation, six within a few months, two others were discharged almost moribund, and four are still alive. The remaining two were untraced. Two patients received deep x-ray therapy following nephrectomy. One of these is still alive nine months afterwards.

SUMMARY OF CLINICAL FINDINGS

NO.	AGE IN YEARS	SEX	PRESENTING SYMPTOM	SIDE OF TUMOUR	TREATMENT	CLINICAL COURSE (from onset)
1	$\frac{2}{12}$	M.	Loss of weight.	R.	None.	D. in less than 2 mth.
2	$4\frac{2}{12}$	F.	Enlargement of abdomen.	R.	Nephrectomy.	D. in 4 mth.
3	$1\frac{1}{12}$	M.	Abdominal pain and vomiting.	L.	Nephrectomy.	D. in 9 mth.
4	$2\frac{11}{12}$	M.	Loss of weight.	L.	Nephrectomy.	A. 14 mth. from onset, 8 mth. after nephrectomy (1938).
5	$4\frac{9}{12}$	M.	Haematuria, 4 days only.	L.	Laparatomy. Biopsy only.	D. in 7 mth.
6	5	F.	Acute abdominal pain and fever—3 days.	L.	Nephrectomy.	D. in 3 mth.
7	$3\frac{10}{12}$	F.	Swelling of the abdomen.	L.	Nephrectomy.	A. and well 6 mth. after nephrectomy (1934).
8	2	F.	Enlargement of abdomen.	R.	Nephrectomy.	Untraced.
9	$1\frac{7}{12}$	F.	Haematuria, 3 weeks.	R.	Nephrectomy.	A. $4\frac{1}{2}$ yr, from onset.
10	$\frac{11}{12}$	M.	Enlargement of abdomen.	L.	Nephrectomy.	D. at age of $1\frac{4}{12}$.
11	2	F.	Enlargement of abdomen.	L.	Nephrectomy.	Fate not definitely known. but was going downhill when discharged.
12	$7\frac{6}{12}$	F.	Abdominal swelling. Pain in the R. loin.	R.	Laparotomy only.	D. in 6 mth.
13	$4\frac{1}{12}$	F.	Epigastric pain and vomiting—1 week.	L.	Laparotomy only.	D. in 1 mth.
14	$3\frac{2}{12}$	M.	Haematuria.	R.	None.	D. two days after admission. Onset indefinite.
15	$1\frac{6}{12}$	F.	Swelling left side of abdomen.	L.	Nephrectomy.	A. $8\frac{1}{2}$ yr. from onset.
16	$2\frac{8}{12}$	F.	Vomiting, blood in the stools—3 days.	L.	Nephrectomy.	A. $11\frac{1}{2}$ yr. from onset.
17	$2\frac{4}{12}$	F.	Enlargement of abdomen.	L.	Nephrectomy.	D. in 1 mth.
18	$3\frac{3}{12}$	F.	Abdominal pain.	L.	Nephrectomy.	Fate not definitely known. Had secondaries in the loin.
19	$\frac{11}{12}$	M.	Enlargement of abdomen.	R.	None.	D. in $3\frac{1}{2}$ mth.
20	$1\frac{4}{12}$	F.	Vomiting—blood in stools—36 hours.	R.	Nephrectomy.	D. in $7\frac{1}{2}$ mth.
21	$2\frac{4}{12}$	M.	Vaguely unwell—6 mth.	L.	None ; too ill for operation.	D. in 6 mth.
22	$2\frac{2}{12}$	M.	Enlargement of abdomen.	B.	None ; inoperable on admission.	D. in 6 mth.
23	$8\frac{4}{12}$	F.	Abdominal pain and fever.	R.	Laparotomy. Biopsy only.	D. in about 6 mth.
24	$2\frac{5}{12}$	F.	Enlargement of abdomen.	R.	Laparotomy; tumour inoperable.	D. in $3\frac{1}{2}$ mth.
25	$6\frac{4}{12}$	M.	Haematuria—1 week.	L.	Nephrectomy.	Untraced.
26	$3\frac{5}{12}$	F.	Abdominal pain.	L.	Nephrectomy.	D. in $4\frac{1}{2}$ mth.

A.=Alive. D.=Died.

Duration of life.—Of those known to have died only three lived for more than six months after the appearance of the first symptoms, the longest period being nine months. The average was five months. Several died within three months of the onset. The fate of five patients could not be traced. Two of these had extensive secondaries on discharge and may be presumed to have died soon after, and another was alive and well six months after nephrectomy in 1934; four children are known to be alive, one four years after operation, another eight years, and another eleven years, while the most recent case is still alive nine months after nephrectomy.

Diagnosis.—The diagnosis in most cases is easy. The tumour in one or other flank is usually easily palpable. It may be confused with unilateral hydronephrosis, especially if this is very tense. Pyelography will generally exclude hydronephrosis. It may sometimes be difficult to distinguish a Wilms' embryoma from a suprarenal sympathoblastoma. In the latter the growth tends to extend more to the mid-line and is more fixed. There are often secondaries either in the liver or bones, especially those of the skull. If bony metastases are present a diagnosis of sympathoblastoma may confidently be made, as the renal tumour hardly ever metastasizes in bone. Dean and Pack (1932), however, reported two cases in which metastases had occurred in the scapula, parietal bones and ileum.

Treatment.—The tumour is in most cases well encapsuled and not very adherent to surrounding tissues. Removal is, therefore, not difficult. Unfortunately recurrence is very common. The site is usually in the operation bed, but metastases in the viscera, for example the liver and lungs, occur in some 20 per cent. of cases. Lately, especially in America, it has been the practice to irradiate the growth before and after operation. The Wilms' embryomata are very radio-sensitive and diminish considerably in size as a result of x-ray therapy (Dean and Pack, 1932). Thorough treatment of this kind, therefore, might diminish considerably the proportion of recurrences.

Morbid anatomy

The tumour was on the left side in fifteen cases, on the right in ten and in one both kidneys were stretched over a large tumour. These growths are usually solid, encapsulated, and press upon rather than invade the kidney—which is, however, often compressed into a thin sheet or strip stretched over the tumour. On section fibrous septa may be seen dividing the tumour into lobules, but these are not constantly present. The consistency is not uniform; in the same tumour may be found dense fibrous areas, parts firm and elastic, massive areas of haemorrhage, recent or of some duration, with soft, gelatinous areas surrounding the haemorrhages. The confluent necrotic areas which are seen in most tumours of the sympathetic nervous system arising from the suprarenals were not present in this series of Wilms' embryomata.

Two tumours were cystic. Projecting into the cavity of one was a large, papilliferous tumour mass. A smaller ingrowth from the wall of the cyst was solid and had a smooth surface. The cyst appeared to grow from the region

of the pelvis of the kidney, but histologically the solid parts of the tumour were indistinguishable from other tumours in this series (see fig. 2, 3 and 4). The other contained thick grumous material, probably a degeneration product, while the only solid parts of the tumour were at the periphery of the cyst where haemorrhagic and semi-solid tumour substance could be recognized. Only the upper pole of the kidney could be identified, but between this and the tumour cyst was a fibrous capsule. The more solid portion showed the microscopical appearances of a typical Wilms' embryoma.

Direct extension of the growth was observed in one of the cases which came to post mortem and in one operation case. In the former the growth extended

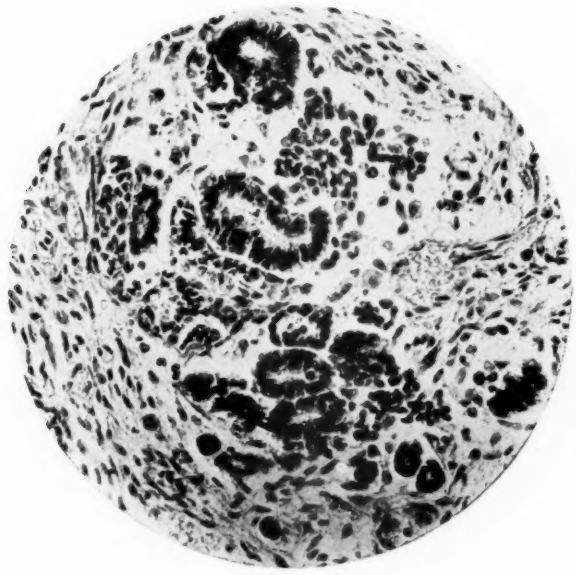

FIG. 1.—A representative section from case 6. Numerous tubules varying greatly in size and shape are present. Some have practically no lumina. On the left is a band of spindle cells running almost vertically. Two groups of small undifferentiated cells may also be seen. (Stain : Haematoxylin and Van Gieson ; × 220.)

not only into the renal vein but also up into the inferior vena cava. Mr. O. L. Addison, F.R.C.S., operated on the other case and has kindly furnished details of his operative findings. The growth extended around and down the upper part of the ureter. The diseased portion of the ureter was removed together with the kidney and the growth, but it is certainly surprising that the child is still alive four-and-a-half years after operation, especially as no subsequent x-ray treatment was given.

Metastases in the glands directly draining the renal area were present in twelve of the twenty-six cases. It is obviously idle to speculate on the likelihood of visceral metastases in cases in which no post mortem was held ; it is only possible to mention if enlarged or obviously invaded glands were noted by the surgeon at operation. At post mortem visceral metastases were commonest in the lungs ; they were present in three cases of the ten which came to autopsy.

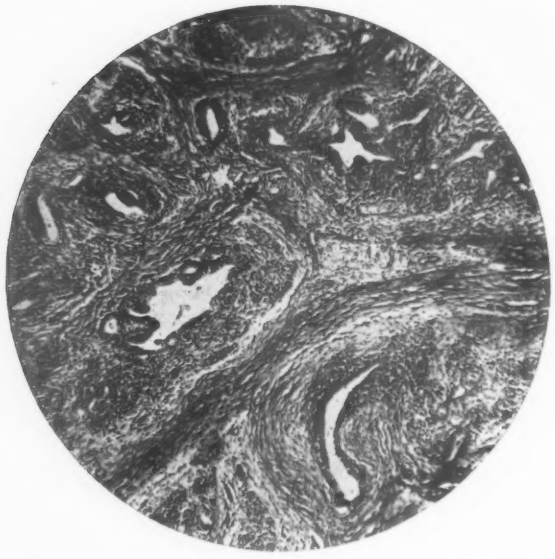

FIG. 2.—Low-power view of tumour from case 15. (Child alive eight years after operation.) Many tubules, some dilated, are seen surrounded by small undifferentiated cells. A broad band of connective tissue passes right across the section. (Stain : Haematoxylin and Van Gieson ; × 50.)

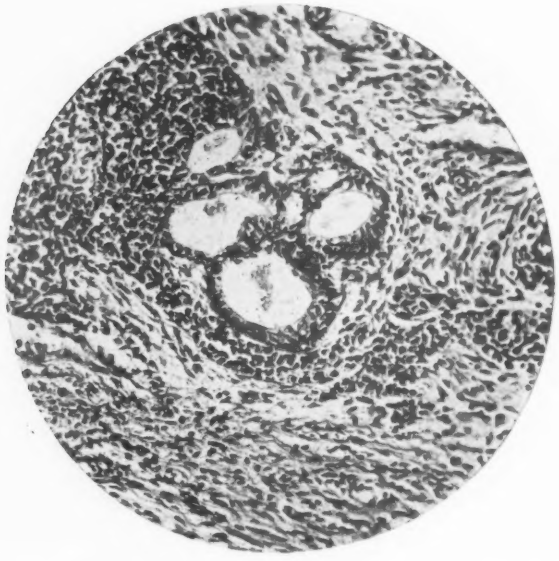

FIG. 3.—Higher power view of tubules from same tumour. A group of tubules merges into a mass of small undifferentiated cells. The tubules are lined by a low cubical epithelium and in several of them there is reduplication of the lining cells. A definite basement membrane is present. Several of the tubules contain hyaline material. (Stain : Same as fig. 2 ; × 150.)

FIG. 4.—High-power view of tubules in another section from same case showing proliferation of layers of cells lining the tubules and a columnar type of epithelium. (Stain : Same as fig. 3 ; × 225.)

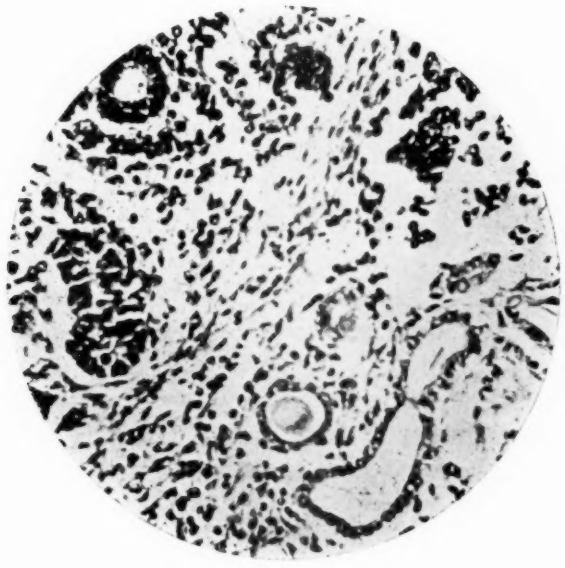

FIG. 5.—Section from case 19 to show two types of tubule. The two lower tubules are lined by a single layer of cubical epithelium and one of them contains hyaline material. The two upper tubules have a taller epithelial lining and this is several layers in thickness—see fig. 6. (Stain : Haematoxylin and eosin ; × 150.)

In two cases in which operation was performed the symptoms and x-ray findings left no doubt that the lungs were invaded by secondary deposits. One of these children died seven-and-a-half months after operation ; the other could not be traced, but he left hospital in such a poor condition that he was not expected to survive more than a few weeks. Tiny metastases barely visible to the naked eye were found in the liver at post mortem in two cases. The diaphragm was observed to be invaded by growth in one case at post mortem and in one case at operation. These findings confirm those of other authors that visceral metastases are relatively uncommon. In Wilms' review of the

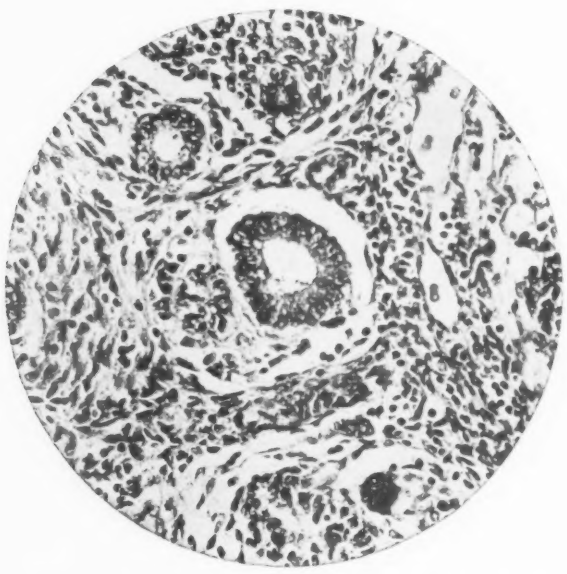

FIG. 6.—High-power view of one of the tubules seen in fig. 5. Reduplication of the cells lining the tubule can be seen. A definite basement membrane is present. Spindle cells and small round cells surround the larger tubule forming a kind of " capsule " in which the tubule lies. (Stain : Same as fig. 5 ; × 220.)

literature he found visceral metastases in 30 per cent. of cases. Lyman (1925) put the figure as high as 50 per cent., whereas Wollstein's figures were three out of seventeen.

Histological findings.—In nine tumours of the series sufficient material was available for a detailed study of the histology. That is to say, sections taken from various parts of the tumours were stained by a variety of methods, including iron haematoxylin with Van Gieson's counterstain and Foot's method for reticulum, in addition to the routine method of haematoxylin and eosin. In the other cases sections stained by the routine method only could be studied, but as a rule several different sections were available from each case, enabling a fairly representative picture of the particular tumour to be reconstructed.

The general characteristics of the tumours differed little from those which have previously been recorded. Although the histological appearances varied in different parts of the tumours it was possible in almost every case to find one

or two areas which served to identify them as embryomata. The most common picture was that in which solid, irregular masses of undifferentiated spindle cells, oval cells or round cells with little cytoplasm lay in a loose fibrillar matrix, the masses being separated one from the other by strands of connective tissue. In sections stained with Foot's reticulum stain it was possible in some cases to demonstrate fine reticular fibrils between the cells, especially when these were arranged somewhat loosely. The arrangement of these masses of undifferentiated cells varied from case to case. Sometimes they were arranged in a lobulated pattern, sometimes there was little connective tissue present and the masses of cells gave an appearance strongly suggestive of a sarcoma. In the midst of these undifferentiated cells various types of tubule were found on which the diagnosis of embryoma was based. In some cases tubules were numerous ; in others they were scanty and few would be seen in one section. There was great variety in the size and shape of these tubules. Fig. 1 is representative of the common forms observed. In this tumour most tubules were lined by one or more layers of columnar epithelium. Many were twisted, giving a U-shaped appearance. The difference in size is well seen in the photomicrograph. Some of these tubules contained granular material staining yellow in Van Gieson's stain and pink in eosin. The tubules possessed a definite basement membrane. In some there was a ' heaping up ' of proliferating epithelial cells at one side of the tubule, as for example in fig. 4. Cystic dilatations were not usually observed in this type of tubule. Other types are shown in figs. 2, 3 and 5. In these, cystic dilatation was common and the dilated tubules often contained masses of hyaline material. The epithelium of these tubules was cubical in shape and only rarely was it more than one layer in thickness. Tubules with low cubical epithelium were found singly rather than in groups. The appearance shown in fig. 3 was therefore the exception rather than the rule. Fig. 5, which shows two isolated tubules with flattened epithelium, one containing a hyaline mass, is much more typical. So far, the histological findings agree with those of McCurdy and others who have described the characteristic tubules of these tumours. Where the findings in the present series differ is in the almost complete absence of striped muscle fibres. In spite of careful scrutiny of a number of sections we were able to find definite smooth muscle fibres in only one case (no. 16). In this, diligent search revealed a small bundle of smooth muscle fibres. As the percentage of cases in which smooth muscle fibres are present has been variously estimated from 10 to 37 (McCurdy), we are quite at a loss to explain their absence in our series. Primitive glomeruli were uncommon. They were best seen in the case of the three-month-old baby which is being reported separately by Dr. D. N. Nabarro.

Histological examination of the metastatic deposits in the lungs and liver showed only undifferentiated spindle-cells and small round cells with scanty cytoplasm, many of which were undergoing mitosis. A variable amount of fibrous tissue was present in these deposits, but the characteristic tubules could nowhere be seen.

FIG. 7.—Case 16 : solid fibrous-looking tumour with the lower part of the kidney stretched out over the surface. The child is alive eleven years after nephrectomy.

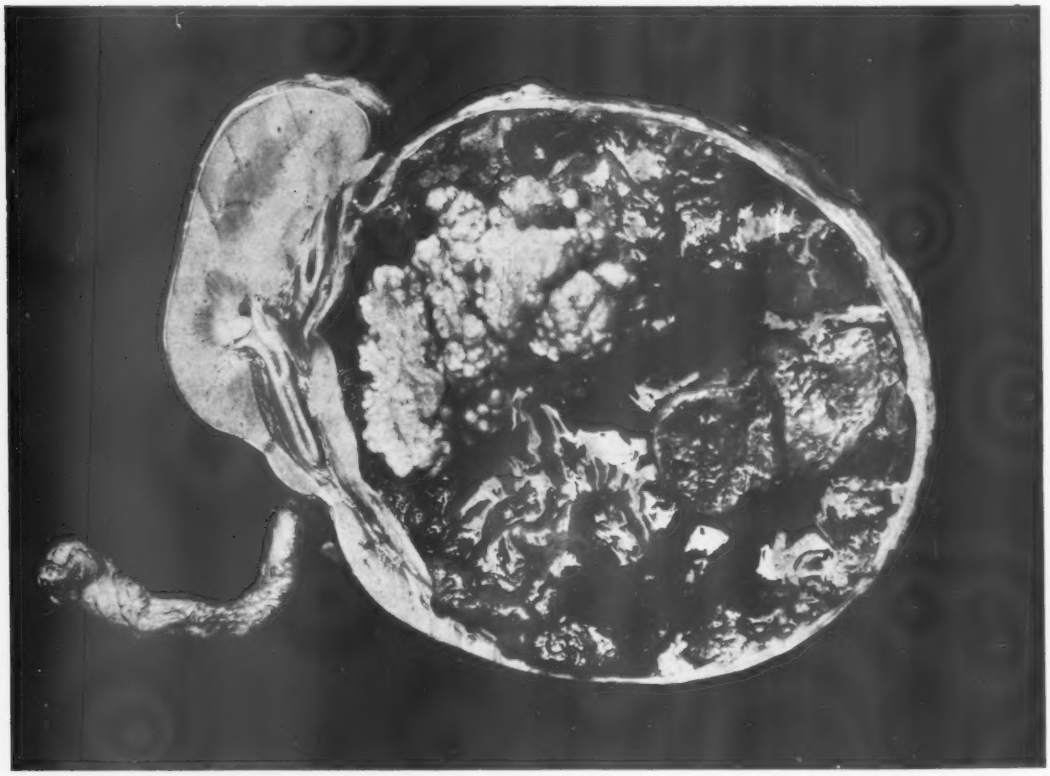

FIG. 8.—Case 15 : one of the two cystic tumours into which there projects a large papilliferous ingrowth. The kidney lies to the left of the cyst. This child is alive eight years after nephrectomy.

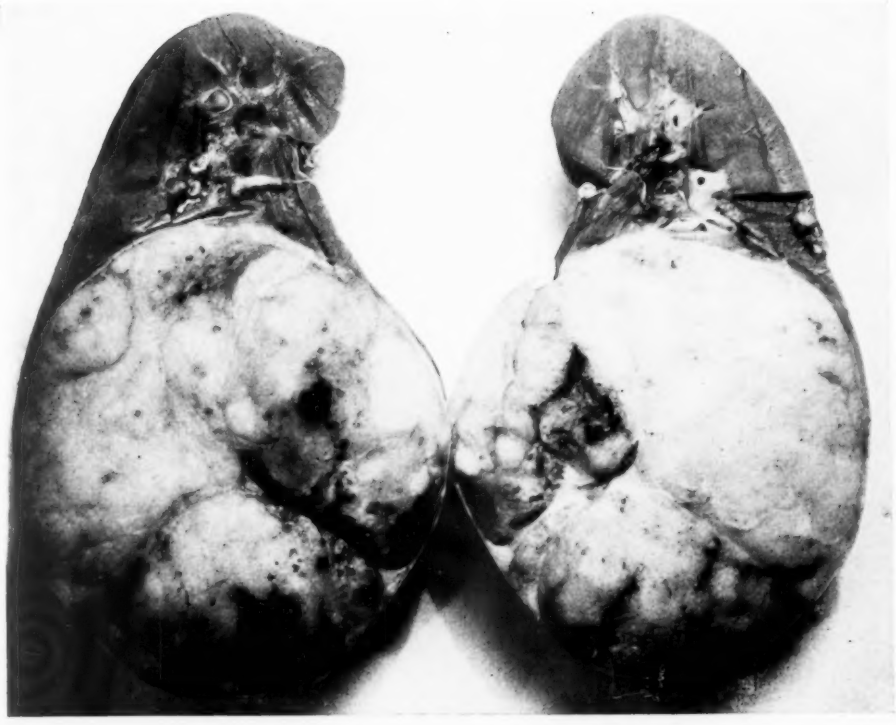

FIG. 9.—Case 3 : firm solid tumour into which haemorrhages have occurred. The child died within a few months of operation.

FIG. 10.—Case 4 : solid fibrous-looking tumour. Child still alive eight months after nephrectomy.

Discussion

Wilms' embryomata are among the commonest malignant tumours met with in children. They occur as frequently as the sympathoblastoma arising from the sympathetic nervous system. During the years 1921 to 1936 inclusive twenty-five cases of the latter occurred at the Hospital for Sick Children, Great Ormond Street. The series of twenty-six cases described in this paper includes

FIG. 11.—Case 6 : gelatinous tumour with many fibrous septa and containing areas of haemorrhage.

the year 1937. These figures contrast with those for other types of malignant abdominal tumours, of which only four examples were traced over the same period. These were diagnosed as retroperitoneal sarcomata, and histological examination confirmed this diagnosis.

The onset is usually insidious and the disease may be far advanced before the patient is brought to the doctor. Enlargement of the abdomen is the commonest presenting symptom, but haematuria is uncommon either as an early or late symptom. This observation has been made by many writers and is

explained by the fact that the kidney is compressed but rarely invaded. The tumour was in most cases well encapsuled and easily removable.

Unfortunately in many of the patients there was a recurrence of the tumour

FIG. 12.—Case 6 : thoracic viscera showing massive secondary deposits in the lungs.

within several months after operation. These recurrences were usually in the loin or neighbouring lymphatic glands and in a few cases in the viscera, especially the lungs and liver. Of the sixteen patients who had a nephrectomy, four are still alive eleven years, eight-and-a-half years, four-and-a-half years, and eight months respectively after operation. The first three patients may reasonably

be considered cured. It is too early yet to say whether in the remaining one there will be a recurrence. This patient had post-operative x-ray therapy ; the others did not. This recovery rate compares favourably with that of 12·3 per cent. in the review by Prather and Crabtree of one hundred cases, and is decidedly better than that of Geschickter and Widenhorn, who followed

FIG. 13.—Specimen removed after seventeen doses of deep x-ray therapy. Notice the fibrous appearance of the tumour. (Photograph from a private case reproduced by courtesy of Mr. T. T. Higgins.)

up twenty-five patients and found not one alive five years after operation. Work in America has raised the hope that better results might be obtained by irradiation of the tumour both before and after nephrectomy. There is no doubt that these tumours are very radio-sensitive and will shrink considerably in size after exposure to deep x-rays. Mr. T. T. Higgins, F.R.C.S., has kindly allowed us to quote a case of his which had seventeen treatments with deep x-ray

therapy followed by nephrectomy. The appearance of the tumour (fig. 13) was very fibrous and on section dense fibrous tissue had completely replaced the tumour cells.

Summary

(1) A series of twenty-six cases of Wilms' embryoma of the kidney is described covering a period of seventeen years.

(2) The tumours were one-and-a-half times as common in females as in males. All but three of the patients were below the age of five years and fifteen were under three years.

(3) The growths were commoner on the left than on the right. One occupied a median position and had both kidneys stretched over it.

(4) The onset was in most cases insidious, the commonest presenting symptom being enlargement of the abdomen.

(5) In seven cases the onset was acute or subacute.

(6) Visceral metastases were uncommon, occurring in only a third of the patients who came to autopsy, and these were not extensive.

(7) The results of nephrectomy in this series are encouraging, as of the sixteen patients operated on, four are still alive.

(8) It is suggested that a more hopeful prognosis may be given if patients are subjected to nephrectomy preceded and followed by deep x-ray therapy.

It is a pleasure to thank Dr. D. N. Nabarro, Director of the Pathological Department, for his advice and encouragement. We are grateful to the Honorary Staff of the Hospital for permission to use their case records and especially to Mr. T. T. Higgins for kindly furnishing us with additional details of several cases. To Mr. Addison, Honorary Consulting Surgeon, who operated on many of the cases recorded, we are particularly indebted for information about the subsequent history of his cases. All the photographs were taken by Mr. D. Martin, who has also helped considerably in collection of material for the pathological part of this paper, for which we thank him.

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OESOPHAGITIS IN INFANCY

BY

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(From the Children's Hospital, Birmingham)

The majority of text-books dealing with diseases of children, written during the past fifty years, describe oesophagitis as an inflammation which occurs : (*a*) as the result of mechanical or chemical irritation, (*b*) in the catarrhal stage of the specific fevers, (*c*) rarely as an extension of an infection in the mouth and (*d*) occasionally spontaneously in young infants. During infancy oesophagitis does not seem to have attracted much attention. Its presence in a number of post-mortem examinations in infants and the recognition of this disease in a number of infants during hospitalization have provided sufficient material to make a brief survey of the condition. A review of the records of the Birmingham Children's Hospital for the past three years shows that whereas thirty-one children have been admitted for treatment of foreign bodies in the oesophagus, poisoning and congenital strictures, twenty-eight children have died with an acute oesophagitis. The age of the former group was between one and twelve years. Those cases of acute oesophagitis in the latter group were under ten months of age, the average being four months.

Twenty-eight cases of acute oesophagitis are classified in the following table according to their etiology.

Table 1

THRUSH	22
NON-SPECIFIC	3
DIPHTHERIA	2
TUBERCULOSIS	1
VINCENT'S ORGANISM	1

Those cases recorded as non-specific were found to have ulceration and inflammation of the oesophagus without a specific organism or etiological agent being demonstrated.

Table 2 has been compiled to record the cases with the age, chief complaint, important clinical points and principal pathological findings.

Clinical features

Although the complaint of pain beneath the sternum or on swallowing cannot be made by infants, nevertheless the outstanding observation of the mother or nurse in acute oesophagitis in infants is that the infant cries during

Table 2

OESOPHAGITIS—CASE RECORDS

CASE	AGE	ADMISSION DIAGNOSIS	CHIEF COMPLAINTS	OTHER SIGNS	PRINCIPAL POST-MORTEM FINDINGS
1 D.B.	6 wk.	? Pyloric stenosis.	Vomiting—sometimes forcible.	Regurgitations. Toxaemia. Slight thrush on palate.	Sloughing grey exudate on oesophagus. Terminal broncho-pneumonia.
2 B.G.	9 mth.	Vomiting.	Vomiting after feeds—after swallowing.	Occasional haematemesis. Melaena. No thrush.	Ulceration and scarring lower end of oesophagus—ulcers in upper. Terminal pneumonia.
3 G. A.	9 mth.	Pneumonia.	Cough. Vomiting. Refusing food.	Otitis media. Dehydration. Toxaemia. Thrush on palate.	Thick grey exudate over surface of whole oesophagus, palate and larynx. Haemorrhagic areas in lungs. Necrotic bone in mastoid region.
4 D. G.	2 mth.	Marasmus. Feeding problem.	Refusing feeds. Vomiting.	Tube feeding and stomach washouts. Toxaemia—seemed dead several times. Irregular pulse. Thrush in mouth.	Thick grey exudate over whole surface of oesophagus. Gastro-enteritis. Terminal pneumonia.
5 W. S.	4½ mth.	Fibroma of arm. Stomatitis.	Vomiting soon after admission. Stomatitis.	Blood in stool. Diarrhoea. Thrush in mouth.	Oesophagus covered with yellow exudate-like fungus. Also on larynx. Otitis media.
6 J. H.	2 mth.	Marasmus.	Stomatitis. Vomiting.	Respiratory stridor. Offensive breath. Weak pulse. Thrush in mouth.	Oesophagus covered with grey exudate. Ulcers on palate and tongue. Thrush. Marasmus. Gastro-enteritis.
7 B. B.	2½ wk.	Stomatitis. Gastro-enteritis.	Refusal of feeds. Vomiting. Choking.	Dehydration. Stomatitis. Cyanosis. Thrush in mouth.	Vaginitis (thrush). Ulcers of soft and hard palate. Superficial exudate on oesophagus. Gastro-enteritis. Subarachnoid haemorrhage in left parietal lobe.
8 J. R.	2 mth.	? Pyloric stenosis.	Projectile vomiting since birth. No tumour felt. Refusal of feeds.	Vomiting continued. Toxaemia. Weak, irregular pulse. Thrush on tongue.	Ulceration and membrane lower one-third of oesophagus. Otitis media. Cultures—thrush. Klebs-Loeffler bacillus.
9 S. D.	9 mth.	Vomiting.	Vomiting after feeds two weeks—forcible. Convulsions.	Developed signs of tuberculous meningitis. No thrush.	Three small ulcers of oesophagus just below level bifurcation of trachea, one connecting with left main bronchus. Caseating mediastinal glands. Miliary tuberculosis.
10 V. H.	3 mth.	Malfeeding.	Vomiting—delayed.	Terminal gastro-enteritis. No thrush.	Oesophagus coated with thick, cheesy exudate. (Thrush cultured.)
11 B. M.	5 mth.	? Pyloric stenosis.	Vomiting after feeds ; frequent regurgitations. Refusal of feeds.	Dehydration. Toxaemia. Refusal to swallow. Thrush in mouth.	Oesophagus congested, with thick grey membrane. Marked injection of stomach and intestines.
12 D. C.	2½ mth.	Pyloric stenosis.	Operation. Vomiting stopped. Condition improved.	Vomiting returned. Dehydration. Raised pulse. Terminal diarrhoea. Thrush on tongue and palate.	Superficial ulceration of oesophagus (thrush). Gastro-enteritis.
13 J. S.	8 mth.	Scurvy.	Thrush—two weeks. Refused feeds. Pain in legs.	Vomiting. Pale, toxic appearance. Thrush in mouth.	Oesophagus completely covered by soft, thick, white exudate. Mastoiditis. Scurvy.
14 M. A.	2½ mth.	Thrush. Malnutrition.	Refusal of feeds. Dehydration. Weak, irregular pulse and respirations.	Comatose. Blood in vomitus. Thrush in mouth.	Injection of oesophagus. No ulceration or membrane. Severe stomatitis.
15 S. H.	2 mth.	Vomiting.	Copious vomiting since birth. No evidence of pyloric stenosis.	Dehydration and pallor. Refusal of feeds. Irregular pulse. Thrush in mouth.	Thick plaques of greyish white exudate on oesophagus.
16 J. H.	2 mth.	Diarrhoea and vomiting.	Refusal of feeds. Poor colour. Frequent vomiting.	Irregular pulse. Thrush on tongue and cheeks.	Oesophagus covered with white patches of thrush. Congestion and ulceration. Thrush in trachea.
17 B. L.	3 mth.	Vomiting.	Operation for pyloric stenosis. Vomiting stopped. Returned to hospital for vomiting.	Poor colour. Diarrhoea. Thrush in mouth.	Grey exudate in mouth, throat, larynx and oesophagus.
18 A. D.	3 mth.	Gastro-enteritis.	Vomiting frequently during and after feeds. Otitis media.	Extreme toxic appearance. Thrush on tongue and in ear.	Thrush exudate in oesophagus. Necrotic bone in mastoid region. Small ulcers in intestine. Terminal meningitis.
19 R. B.	3½ mth.	Diarrhoea and vomiting.	Vomiting. Discharging ears. Cough.	Blood-stained vomitus. Blood in stools. Toxic. Irregular pulse. Poor colour. Thrush in mouth.	Oesophagus red and injected. Patches of thrush. Thick grey exudate in mastoid antrum. Ulcers in colon.
20 J. M.	5 mth.	Vomiting. ? Pylorospasm.	Several attacks of ? colic. Severe vomiting.	Operation. No pyloric tumour found. Screaming with pain in abdomen one to two hours after feeds. Relieved by food. Blood in vomitus. No thrush.	Oesophagus inflamed. Small superficial ulcers. No exudate.
21 By A.	6 wk.	? Pyloric stenosis.	Vomiting since birth—projectile. Blue spells.	Loss of weight. Terminal diarrhoea. No thrush.	Oesophagus inflamed. Ulceration and dilation at cardiac end. Otitis media.
22 B. A.	10 wk.	Pneumonia.	Vomiting. Dehydration. Collapse.	Refusal of feeds. Pallor. No thrush.	Patches of thrush in oesophagus. Atelectasis.
23 B. P.	9 mth.	Pneumonia.	Refusal of feeds. Cough. Foul sputum. Vomiting. Collapse.	Thrush in mouth treated. Rapid respirations. Toxaemia.	Superficial exudate in patches in upper oesophagus. Middle portion clear. Cerebral sinus thrombosis. Mastoiditis.
24 G. M.	2½ mth.	Pyloric stenosis.	Operation. Vomiting continued. Projectile.	Terminal diarrhoea. Thrush in throat.	Superficial brown exudate on wall of oesophagus. Otitis media. Gastro-enteritis.
25 J. H.	6 wk.	Pyloric stenosis.	Operation. Vomiting continued. Dehydration. Blood in vomitus.	Thrush of mouth treated. Collapse. Toxaemia.	Superficial thrush exudate in oesophagus, throat and larynx. Gastro-enteritis.
26 D. K.	8 yr.	Laryngeal diphtheria.	Croup.	Vomiting.	Diphtheritic membrane on tonsils, larynx and upper part of oesophagus. Myocarditis.
27 B. J.	4 mth.	Vomiting.	Successful operation intussusception. Refusal of feeds.	Re-admitted vomiting. Dehydrated. Poor colour. Discharging ear. Toxic. Thrush in mouth, ear and stool.	Thrush exudate in oesophagus. Otitis media. Gastro-enteritis.
28 H. W.	5 wk.	Marasmus.	Foul stomatitis. Toxic. Vomiting. Collapse.	Irritable. Rapid weak pulse. Vincent's organism.	Oesophagus congested. Greyish-brown exudate over lower one third.

the act of swallowing or immediately after it swallows, or that it refuses to feed. Many of the infants in this series would take the liquid into the mouth and then allow it to dribble from the corners. The chief complaint was vomiting, this

FIG. 1.—Case 8. Oesophagus and stomach. Ulceration and membrane. Diphtheria and thrush.

being of a particular type in that the food if swallowed was vomited back either as an immediate regurgitation of the food taken or as a large, forceful vomit during, immediately after or within a short time after the feed. The forceful vomiting has resulted in several infants being suspected of having pyloric

stenosis. Eleven infants were investigated with this condition in mind. In four cases of pyloric stenosis, thrush oesophagitis followed the operation. Projectile or forcible large vomits were noted in six other infants in this group.

Blood was noticed in the vomitus of nine infants and melaena was present in four. Dark brown vomitus occurred in several others and suggests that blood was present in them also. Blood was seen in the vomitus of all three of the so-called non-specific cases of oesophagitis (cases 2, 20 and 21). The following short summary of the records of case 2 illustrates the type of course which the non-specific group followed.

Case 2, B.G., aged nine months, was admitted to the hospital with the history that he had had frequent attacks of vomiting since birth. There had been very little gain in weight. (Admission weight—14 lb. 6 oz.) Small amounts of blood had been noticed in the vomitus on several occasions. The infant improved in the hospital for several days, being fed small frequent quantities of milk during the day and night. However, after one week the vomiting returned and definite melaena was noted. The vomitus was blood-tinged. The child was very irritable between feeds and often cried as though in pain. It was noticed that the vomiting occurred immediately after the first swallow of food and suggested some abnormality of the oesophagus. The infant's general condition rapidly deteriorated and death was due to terminal pneumonia. At post mortem the lower end of the oesophagus was scarred and covered with chronic ulcers. A few small ulcerated areas were present in the middle portion of the oesophagus.

Similar ulceration was found in case 20—an infant of four-and-a-half months who had projectile vomiting and screaming attacks. The latter would come on one to two hours after feeds and were relieved by taking food. The other infant in this group cried when the food was swallowed and sometimes became cyanosed during the feed, presumably as the result of milk being retained in the pharynx.

Diphtheria of the oesophagus in two children (cases 8 and 26) was the result of direct extension of laryngeal diphtheria. The membrane and ulceration of the oesophagus and larynx in case 8 will be seen in fig. 1. This child also had a superimposed or coincidental thrush infection.

The one child with tuberculosis of the oesophagus (case 9) gave a history of vomiting immediately after food for two weeks. This continued for the two weeks that the child was in hospital, and during this time evidence of generalized tuberculosis was found. Death was due to tuberculous meningitis. At the post mortem three small areas of ulceration were found near the middle of the oesophagus. One of these ulcers formed the opening of a fistula which connected with the left main bronchus. Large caseating tuberculous glands were found in this region and appeared to be the cause of the oesophagitis. A section of the wall of the oesophagus at the site of one of the ulcers is shown in fig. 2.

The oesophagus of the child with Vincent's infection was covered with a brown, stringy exudate which had formed on top of superficial ulcers scattered on the whole surface. These ulcers had clearly marked edges with a surrounding ring of inflammation.

Thrush was the parasitic organism found in the direct smears and cultures

FIG. 2.—Case 9. Tuberculosis of the oesophagus. Section of wall of oesophagus through area of ulceration. × 120. H. & E.

FIG. 3.—Case 27. Section of gelatin culture of thrush. Gram stain ; × 660.

of twenty-two infants with oesophagitis. They had, with a few exceptions, been noted to have oral thrush. Apart from the common symptom of vomiting, these infants with thrush infection presented a clinical picture which seemed to be characteristic in many respects, and enabled a diagnosis of thrush oesophagitis to be made in several cases. A previous history of thrush of the mouth or its presence during examination was usually noted. Refusal to take feeds was a very common complaint, and was presumably due to the sore tongue and

FIG. 4.—Case 12. Oesophagus with patches of thrush and early ulceration.

mouth caused by thrush. In a few infants there was a refusal to swallow, since this appeared to cause marked pain. They were usually irritable. Milk would sometimes be taken into the mouth and would then be allowed to run out with no attempt to swallow. If food was swallowed it was noted in most cases that this was regurgitated immediately. In other cases the milk would be vomited back in a projectile manner or forcibly soon after feeding. Streaks of blood were frequently observed in the vomitus. Dehydration became a serious factor

in the presence of frequent vomiting, and parenteral fluid administration was usually required. The loss in weight sometimes became alarming.

Toxaemia appeared to develop, usually a few days after the onset of severe symptoms. In spite of seemingly adequate parenteral fluid and correction of

FIG. 5.—Case 13. Membrane, ulceration and haemorrhage in thrush oesophagitis.

the dehydration, and without signs of infection elsewhere in the body, these infants would become a pale greyish colour, with cold and sometimes cyanotic extremities. The temperature in some cases was slightly raised, but was often subnormal. The pulse rate was always rapid and usually irregular. The

volume in some cases was so weak that records of pulse could not be made. Respirations were irregular, but usually only became rapid in the terminal stages. Periods of apparent recovery with less vomiting, brighter appearance and colour, alternated with periods when the child appeared to be dying. Diarrhoea was never an outstanding sign. Extension of the thrush infection to the intestines

FIG. 6.—Case 4. Thick white exudate with ulceration and haemorrhage in severe thrush oesophagitis.

was demonstrated in two cases. Terminal broncho-pneumonia occurred in nearly every case.

The predisposing factors in the occurrence of this form of infection are theoretical but certain common facts were noted. All of the infants were artificially fed. Several cases were associated with debilitating conditions, such as pyloric stenosis, otitis media and previous attacks of gastro-enteritis. Stomach wash-outs were employed in eight infants, including the cases of

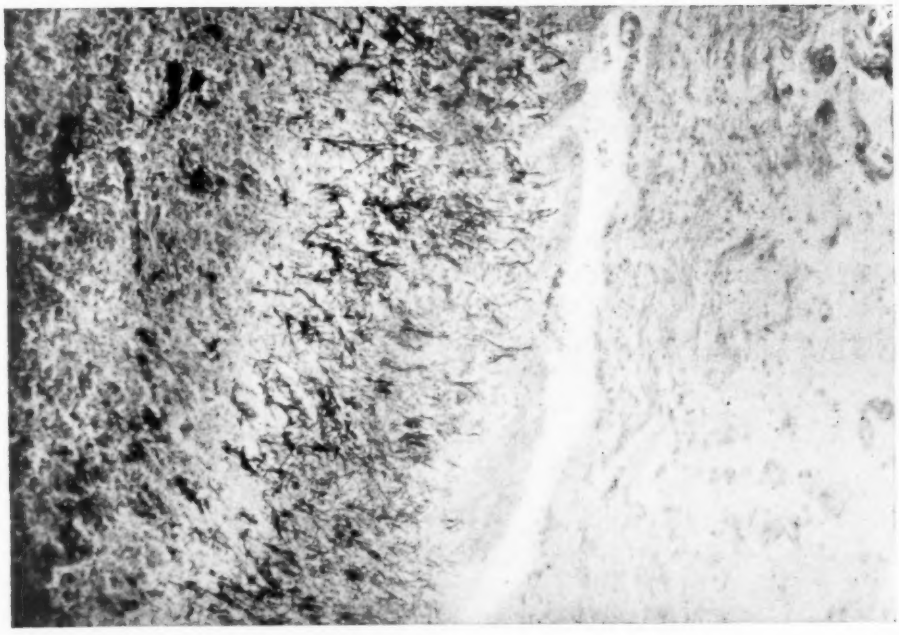

FIG. 7.—Section of wall of oesophagus. Thrush mycelium penetrating the tissues. Gram stain ; × 120.

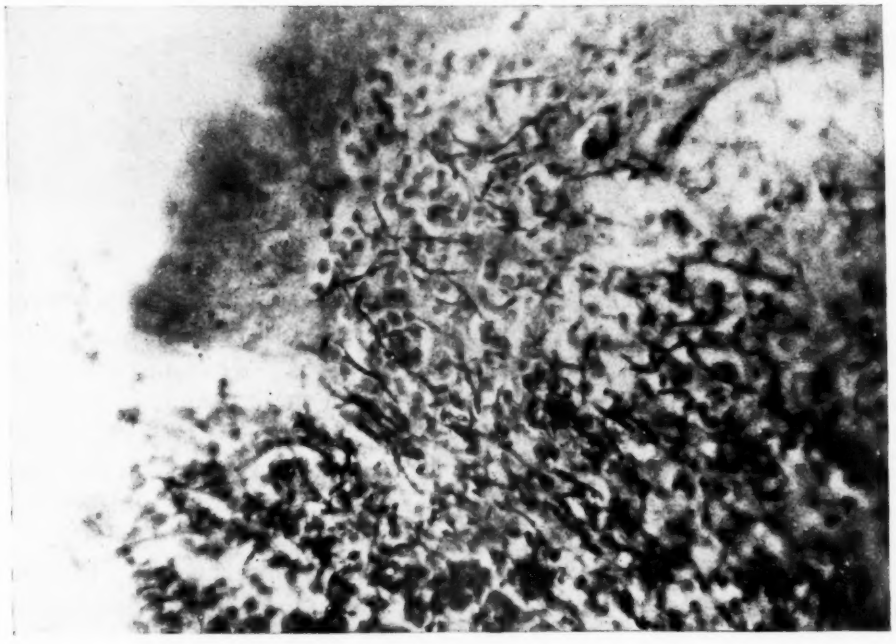

FIG. 8.—Thrush oesophagitis. Ulceration of surface epithelium and growth of mycelium in deeper layers. Gram stain ; × 290.

pyloric stenosis, and the possibility of trauma to the oesophagus, which would allow the thrush infection to become established, cannot be ignored. The passage of any instrument through the mouth of a young infant with thrush appears to be attended by a definite risk of spreading the infection into the oesophagus. This possibility is a serious one in cases of pyloric stenosis.

Pathology

Thrush is a parasitic disease caused by a fungus which has been given a variety of names, but which is commonly called monilia albicans. So-called 'white mouth' is a not uncommon finding in young artificially-fed infants living in poor hygienic surroundings, and is found with many protracted wasting

FIG. 9.—High-power of fig. 8.

diseases of early life. The disease seldom develops on healthy mucous membrane, its growth being favoured by slight abrasions or irritation. It sometimes occurs in mild epidemics in institutional nurseries. While the usual site of thrush is the margin of the tongue, the inside of the lips and cheeks and the palate, it not infrequently involves the whole pharynx and rarely extends down the oesophagus or into the larynx. Small white patches appear in the mouth, which look like clotted milk but which when rubbed off leave small bleeding points. The mouth and tongue is usually dry and slightly inflamed. The infection is a superficial ulceration which is apparently caused by the spores lodging on the surface and then spreading between the different layers of cells. These spores are oval or oblong in shape, about 5μ to 7μ in size, and are readily seen in direct smears from the lesions stained by ordinary methods. The mycelial form of the fungus is a large, bacillary, septate organism 20μ to 30μ

long and 4μ to 5μ in diameter. These organisms grow on the majority of ordinary culture media. A section of a gelatin culture is photographed in fig. 3.

In the oesophagus the lesion is a superficial ulceration with a soft, thick, grey exudate over the surface which can be partially removed fairly easily (fig. 4). The longer the infection has been present the more adherent the exudate becomes, and in a few cases could not be removed without stripping the whole epithelial surface (figs. 5 and 6).

Histological sections of the wall of the oesophagus at the site of the infection show a superficial ulceration with an exudate or membrane composed of spores, epithelial cells and debris. The mycelium can be seen penetrating the wall,

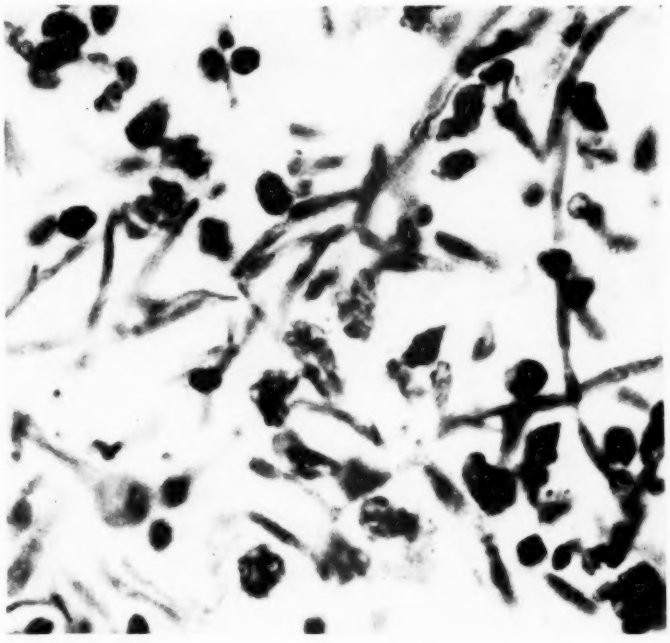

FIG. 10.—Section of wall of oesophagus showing mycelium and spore formation with several degenerating epithelial cells. Gram stain ; × 1100.

lying between the epithelial cells, entering the submucous layer, the muscularis mucosa and in a few cases the muscle coat. The capillaries in the submucosa show marked congestion. (Photographs illustrating the histological picture are shown in figs. 7, 8, 9 and 10.)

Patients with superficial lesions have been described who have had agglutinins in their blood (Gay and others, 1935). Holt and McIntosh (1933) state that thrush may invade the blood and cause thrombosis or be carried to distant parts of the body. Monilia infection has been described in many parts of the body (Eustace Smith, 1884). In the group of patients observed in this series with oral thrush and oesophagitis, there were two infants with small pin-point ulcers in the colon in whose stools large numbers of thrush spores were found. One female infant also had a severe membranous vaginitis which

was due to the same organism, another child had a balanitis, one a conjunctivitis and two with pneumonia had thrush in the lungs. Two with otitis media

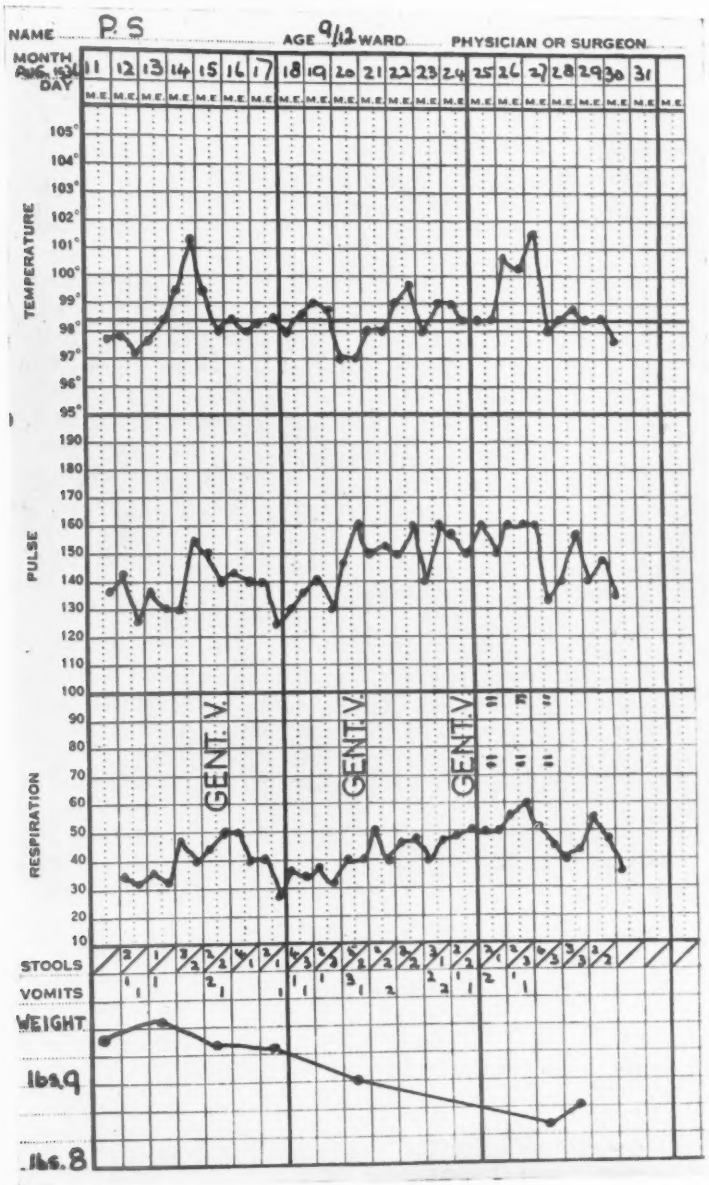

FIG. 11.—Temperature chart of Case P.S. showing clinical course with gentian violet treatment. Gent. V.=mouth painted with gentian violet (1 per cent. aqueous solution).

had large numbers of thrush spores in the discharge, and at post mortem there was a mass of grey purulent exudate and the bone in the mastoid region was necrotic.

Treatment

The treatment of thrush consists in local applications, oral hygiene and attention to the general health of the infant. A 1 per cent. aqueous solution of gentian violet has been found satisfactory in hospital cases. Borax and glycerin has been disappointing. Signs of the disease in the mouth usually disappear after the first application of gentian violet. The only disadvantage appears to be the temporary staining of the lips and mouth. Liberal applications of gentian violet have been applied to the mouth in suspected cases of thrush oesophagitis in the hope that it would reach the affected areas in the oesophagus. The results have been encouraging, as illustrated by the following case record.

P.S., aged nine months, was brought to the hospital for the treatment of a naevus, and on routine examination was found to have thrush, which disappeared after one application of gentian violet. Two days later the temperature became elevated and vomiting commenced for which no adequate cause could be found. Another application of gentian violet to the mouth resulted in the vomiting stopping for two days. It returned again, and since there was no further sign of thrush in the mouth it was thought to be due to some other cause, although none was demonstrated. The child's condition became extremely critical, the skin was grey, frequent vomiting and slight diarrhoea produced dehydration and in spite of adequate fluid therapy the child appeared several times as if she were about to die. Experience with other patients in whom this peculiar toxic appearance associated with vomiting and following a previous history of thrush had been noted, made the diagnosis of oesophagitis likely. Following several liberal applications of gentian violet to the mouth the vomiting became less, the general condition improved and the child was finally discharged in good condition and gaining weight. (See temperature chart, fig. 11.)

An infant who refuses feeds and vomits soon after swallowing, who has had a thrush infection of the mouth, and who shows a deterioration of its general condition, with a toxaemia which is out of all proportion to the signs which are present, should be suspected of thrush oesophagitis and should be treated as such.

Summary

Twenty-eight cases of oesophagitis in infancy have been briefly reviewed. Twenty-two of these were caused by thrush and presented a clinical syndrome in which the outstanding signs and symptoms were the presence of oral thrush, refusal to take feeds, vomiting during or soon after feeding, severe toxaemia, with pallor and weak pulse and in some cases the presence of blood in the vomitus, and in a few melaena. The pathological process was one of ulceration of the epithelium and invasion of the submucosa by the mycelium of the thrush fungus. Two cases of diphtheria of the oesophagus, one of tuberculosis and one due to Vincent's organism were found. Three infants have been classified as non-specific who were found to have ulcers at the lower end of the oesophagus and who had pain during or after feeding. Local treatment of oral thrush with

gentian violet appears to be satisfactory and one case of oesophagitis is described which appeared to respond to this form of treatment. Thrush is not the benign condition which it is commonly thought to be.

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SYMMETRICAL DEGENERATION OF THE NEOSTRIATUM IN CHINESE INFANTS

BY

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In 1934 I described (Verhaart, 1934) three rare cases of cerebral degeneration in Chinese infants, two of them showing extensive symmetrical degeneration in the caudate nucleus and the putamen with formation of large neuroglial nuclei, resembling Alzheimer's cells, while the other case showed the same affection in several parts of the cerebral cortex. For this reason the three cases were compared with the hepato-cerebral degeneration of Kinnier-Wilson and Strümpell-Westphall. It is not certain that these three cases belong to the same type of affection, as there are important differences between them and similar cases in families belonging to the Wilson-pseudosclerosis group, which have not yet been described in Europe. But now I have examined three other cases resembling greatly the second one formerly recorded, and the resemblance is so important that I feel justified in bringing them into one group and in supposing that they have the same etiology.

Case records

The second patient in the above-mentioned paper was a Chinese girl, eight months of age, who for thirteen days had suffered from fever, cough and stiff limbs. She had not been ill before and was entirely breast fed. During the three days before death the patient was in coma, there was rigidity of the neck, but the stiffness of the limbs diminished. At the post-mortem examination the liver showed a severe degree of fatty degeneration, the brain was not oedematous, but the nucleus caudatus and the putamen were softened and somewhat gelatinous on the surface of a section.

When examined by microscope the neostriatum showed large foci of spongious structure, proliferation of the capillaries, increased nuclei of the neuroglia and almost total degeneration of the neurons and white matter (fig. 1) ; normal tissue had all but disappeared. In the globus pallidus neuroglial tissue was somewhat increased in size, but the ganglion cells were

unaffected. In the medial thalamic nucleus and the superior colliculus the same changes were found to a lesser degree.

I have seen the same histological changes three times in the subsequent years. It is now possible, therefore, to unite these four cases in one group and to compare them with each other.

The second child was a Chinese boy T. T. L., born December 29, 1934, who was admitted in the Central Hospital May 29, 1935, having been ill for nine days. He suffered from fever and kept his eyes constantly closed. There was no cough and no diarrhoea. He had been entirely breast fed. The family consisted of four other children who were healthy. During his stay in the hospital no convulsions were seen, respiration was irregular and the patient

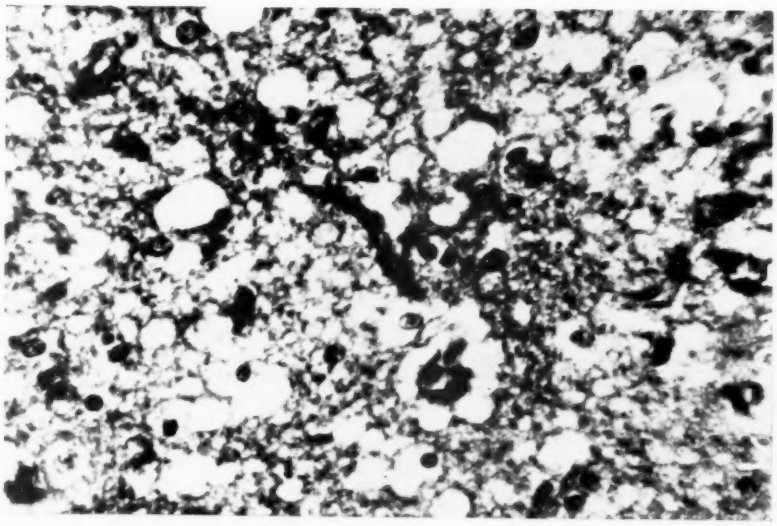
FIG. 1.—Weigert-Pal section of the lenticular nucleus and thalamus of case 1, the myelin sheaths in the putamen have disappeared, but in the globus pallidus and the thalamus they are unaffected.

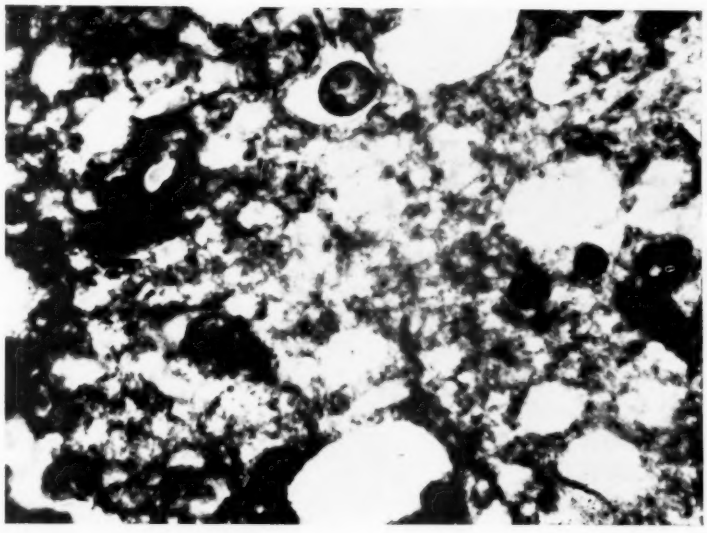
was drowsy. There were no signs of meningitis. The Wassermann reaction was negative in the patient's blood and the blood of his mother. No changes were found in the cerebrospinal fluid ; lead lines could not be detected in the x-ray pictures of the skeleton. Death occurred on June 2, 1935, three days after the beginning of the disease.

At the post-mortem examination a bilateral bronchopneumonia was found with congestion and fatty degeneration of the liver. The brain was normal externally, but on the cut surface the putamen and the caudate nuclei were softened and somewhat gelatinous. In the putamen and caudate nuclei of both sides extensive foci were found, containing vascular proliferation, distended globular neuroglial nuclei, swollen oligo-dendroglia cells and almost total degeneration of the ganglion cells (figs. 2, 3). In the globus pallidus, the corpus subthalamicus and the superior colliculus a small number of similar foci were present, while in the reticular substance of the midbrain, the pons, the medulla oblongata and the spinal cord a relatively large number of swollen neuroglial nuclei were found. In the central grey matter around the iter of

Sylvius the ganglion cells were somewhat degenerated ; they were swollen, contained a great amount of lipofuchsine and the nucleus in many of them was eccentric. Moreover there was a distinct degree of neuroglial proliferation.

In the cerebral cortex there were a small number of rod cells and other





FIGS 2 and 3.—Lower and higher magnification of haematin-eosin sections of the putamen of case 2 ; note the spongious structure.

forms of enlarged microglial cells, and the vessel walls were thickened ; in the white matter the neuroglial nuclei were enlarged, the vessels were engorged. In this case too there was degeneration of the neostriatum with only small foci in some other parts of the central nervous system, an unspecific reaction in the cerebral cortex and fatty degeneration of the liver.

The third child suffering from the same disease was the Chinese girl F. O., five months of age, who entered the hospital one hour before death. She had been ill for eight days with fever and coughing. She was the youngest of five children, two of whom had died ; she was entirely breast fed. At the hospital the signs of bronchopneumonia were found, the nutritional state was good. At the post-mortem examination slight fatty degeneration of the liver was present, the brain was externally congested, on the cut surface the putamen and the caudate nucleus on both sides were yellowish, gelatinous and softened. In the cerebral cortex and white matter the same unspecific changes were found as in the former case, with some small spongious foci around the vessels in the white matter containing some scavenger cells.

The putamen and the caudate nuclei showed the same changes as in the other cases, but there were a small number of extensive foci, extending to the margins of these grey nuclei. In the centre of these foci the tissue was almost

FIG. 4.—Frozen section of the lenticular nucleus of case 4 ; the putamen has been torn because of the presence of softening.

'emaciated,' only a network of glial fibres and small vessels with a small number of scavenger cells remaining. The neuroglia cells were enlarged and resembled Alzheimer's glia cells type two. These cells were larger than those of the former patient without reaching the size of the Alzheimer cells found in cases of pseudosclerosis.

In the other parts of the central nervous system no changes were found, but a small amount of lead was found to be present (9·9γ per gramme dry tissue).

The fourth child was a Chinese boy T. W. H., born January 17, 1937, who at the end of July, 1937, grew weak and almost lost his voice. On August 5, he developed fever and the following day he was admitted to hospital. His temperature was then 39·3° C. ; he was very drowsy and had many convulsions. The tone of the limbs was diminished, the turgor of the skin was bad, there was no rigidity of the neck, the anterior fontanelle was somewhat sunken, the pupils were of normal size and reacted to light. The cerebro-spinal fluid was

clear, Nonne and Pandy's reactions were feebly positive, 5 cells per c.mm. were found ; the Wassermann-reaction was negative, but Meynicke II was feebly positive ; micro-organisms were not found.

The patient had not been vaccinated, his parents and relations were healthy, only talcum powder had been used ; in the x-ray pictures no lead lines were present in the bones. The child had been entirely breast fed. On the day after admission the child died.

On naked-eye examination the central nervous system was quite normal, but at the cut surface the caudate nucleus and the putamen were yellowish and softened (fig. 4).

Microscopically the same changes were found as in the preceding cases, viz. spongious structure with enlargement of the neuroglial cells in the caudate nucleus and the putamen with moderate increase and enlargement of the

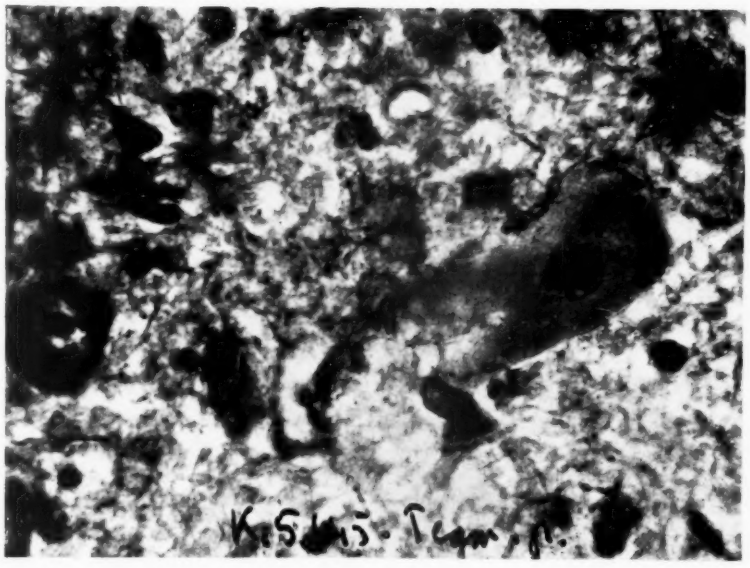


FIG. 5.—Section of the central grey matter in case 4, stained with haematin and eosin ; degenerated and homogenized neuron. The nucleus seen in its centre was found to be situated outside the cell and does not belong to it.

microglia and swelling of the oligo-dendroglia cells. The capillaries were proliferated, some vessels were surrounded by a small number of compound concrements and a small number of vessels by some scavenger cells. The ganglion cells were not in the first place damaged, for nowhere were they totally absent ; even in the most affected spots where the tissue was all but ' emaciated ' some of them could be seen. However, they were diminished in number in whole of the affected grey nuclei, the small ones had lost most of their protoplasm and the big ones were deformed.

In the frontal half of the striatum the changes were most intensive, but the border of the putamen situated near the marrow of the insula was almost unaffected, while in the caudal half only a small spot at the border of the globus pallidus was degenerated. At that place the globus pallidus showed some proliferation of the neuroglia and some breaking-up of the tissue, but everywhere else it was without lesions.

In the cortex and the white matter of the brain no severe changes were

found, but spongious structure and proliferation of the neuroglia were also present in the medial half of the corpus subthalamicum, in the central portion of the red nucleus, in the colliculi and the central grey matter around the aqueduct. In this area severe degeneration of ganglion cells could be demonstrated, a number of them showing total homogenization, in this way changing to large homogenous masses that resembled the neurons only in exterior shape (fig. 5). These were the same changes as in the second child, but to a much more severe degree.

Lead proved to be absent in the central nervous system.

Clinical and pathological summary

Altogether four children have been examined, all of them Chinese infants, eight, five, six and six-and-a-half months of age respectively, who died after suffering for a short period from unspecific cerebral disturbances with coma. Only the first one, the eldest, showed increased tone of the muscles of the limbs ; with the others symptoms of affection of the cerebrum were lacking. All of them were exclusively breast fed, tuberculosis and syphilis could not be found ; lead was demonstrated in a small quantity in the third case, but in the fourth it was absent. Familial or hereditary diseases could not be found; moreover, the second patient was the fifth child out of five, the others being perfectly healthy.

At the post-mortem examination in all of the four cases an extensive symmetrical disintegration of the striatum was found in so typical a manner that in the last case the diagnosis could be made macroscopically. Microscopically a general or localized rarefication of the tissue of the caudate nucleus and the putamen was found with proliferation of the macroglia, which to a greater or lesser degree gave origin to increased naked nuclei, resembling Alzheimer's cells of the second type. The neurons in all cases were scanty, in some of them practically absent ; the capillaries were increased in number, granular cells were present in small quantity, the microglia was increased in size and number, the oligo-dendroglia cells were swollen. To a lesser extent the same changes were found in the globus pallidus, especially at the border of the putamen, the corpus subthalamicus and the red nucleus and the corpora quadrigemina in some cases. In the second and the fourth case ganglion cell degeneration and gliosis were present in the central grey matter, while in the reticular nuclei of the brain stem glial proliferation and a slight degree of rarefication of the tissue existed. In all cases fatty degeneration of the liver proved to be present.

Discussion

It is obvious that these cases show so much similarity, that they must be looked upon as belonging to the same kind of affection and that it is justifiable to suppose the same etiology. In my former paper, in which the first case has already been mentioned, it was put together with two other cases, that differed much more and they were compared with the diseases of the Wilson-pseudo-

sclerosis group. Certainly the four cases here described must be compared with this group, although the typical characteristics must be more critically dealt with than with adult cases. Especially the great neuroglial nuclei, resembling Alzheimer's cells, are much more frequently found in children's brains than in those of adults, a fact that Sterren noted in his thesis in connexion with my former paper. In my Batavian material, consisting of about 100 brains of children below the age of two years, they were found with different diseases, e.g. lead encephalopathy, bacillary dysentery and in cases of convulsions of unknown origin. Fatty degeneration of the liver was also frequently found, but not always ; in some cases of severe fatty degeneration the abovementioned neuroglial nuclei were absent. They were found especially in the pieces of grey matter that connect the caudate nucleus with the putamen and in the latero-dorsal margin of the putamen, while in the deep layers of the cortex and the white matter near to it they were also frequently to be found. The large typical Alzheimer cells, however, were rare, most of the nuclei were only somewhat bigger than the normal ones and the chromatine within the nucleus was scanty. They were not present in normal infants in their typical appearance, but everywhere, especially in the white matter of the cerebral hemispheres, the neuroglial nuclei were bigger and more regularly globular than in adults. In the course of the first year they gradually grow smaller, they contain more chromatin and lose their globular shape in the same measure as the fibre-forming spider cells increase in number. But even at the end of the first year the globular nuclei are still relatively numerous. Therefore it is obvious that with infants the large naked globular nuclei come into existence more easily than in adults, in whom the neuroglia has a tendency to form fibres and a glious scar.

Notwithstanding these facts a comparison of my four cases with Wilson's disease is justifiable because of the extensive symmetrical disintegration of tissue in the neostriatum. Identification will be difficult, since no heredity could be proved, no cirrhosis of the liver occurred and in European families suffering from hepatocerebral degeneration such cases have not been described in infancy. With my cases it is even uncertain that a connexion can be accepted between the degeneration of the liver and the striatum because fatty degeneration so frequently occurs with infants.

In Western literature only a few similar cases could be found, First there is a case by Marinesco and Draganesco (1929) published under the title ' A case of Förster's Syndrome.' A four-year-old child after an infectious disease showed diplegia with athetosis, anarthria and idiocy. When the child was lying, the legs were flaccid, but when the child was trying to stand they were stiffly stretched ; half a year after the beginning of the disease the child developed bedsores and died. At the post-mortem examination fatty degeneration was found in the heart muscle and in the liver ; the putamen and the caudate nucleus were symmetrically brown and atrophic ; in both centra there was disintegration with a slight grade of ' état lacunaire ' and degeneration of the white matter in the globus pallidus at the margin of the putamen. The neurones in the striatum had almost disappeared ; in the frontal part there was a great number of granular cells around the vessels, the micro- and

macroglia had proliferated, glial fibres were formed, the vessels were increased in number, their walls were thickened. In the cerebral cortex the ganglion cells were scanty ; the Purkinje-cells in the cerebellum had also diminished in number.

It is probable that the patients described here would have shown almost the same changes had the disease begun at a somewhat higher age and had the time between the beginning and death been longer. The resemblance is definitely present : the writers cannot find any etiological factor ; they do not think the identity with Wilson's disease absolute, especially because of the affection of the liver.

Icterus gravis neonatorum with ' kernicterus ' of the German writers must be mentioned, but the differences are greater than the similarities. There was no severe icterus shortly after birth and the central grey matter was not stained intensively yellow.

Some similarity is found in the cases described by Paterson and Carmichael (1924) as a familiar degeneration of the lenticular nucleus with a family of twelve children of which only two were healthy. The others died before they were ten months of age with the exception of one, who lived up to two years of age. They all showed cerebral symptoms, the twelfth child was born normally, but soon it grew cyanotic and died three days later. The lenticular nucleus showed proliferation of the vessels and the glia, and small necrotic foci with granular cells occurred. Large irregularly formed glial cells were present, the ganglion cells in the putamen and the globus pallidus had all but disappeared ; in the caudate nucleus two small necrotic spots with granular cells occurred. In the cerebrum and the thalamus unspecific changes were found.

The eleventh child, who died at the age of seven months, showed decreased muscular tone and power, with impaired vision for some months. After death the same changes in the lenticular nucleus occurred, but in the cerebral cortex, especially in the occipital regions, many ganglion cells were missing, while the white matter could only be stained with difficulty. In the substantia nigra, also, the glia and the vessels were proliferated, but the ganglion cells had only disappeared to a lesser degree. The authors are of opinion, that a toxin, circulating in the blood, can be the cause of the degenerations, the peculiar course of the vessels within the lenticular nuclei being the reason of the severe degeneration at that place.

As is obvious, the points of similarity are less than with the patient described by Marinesco and Draganesco (1929), especially concerning the changes in the substantia nigra and the cerebral cortex as well as the familial incidence.

As starting-points for a discussion of the etiology are the facts that the disease began in all of the cases at about six months of age in Chinese children exclusively fed on the breast. At that age breast feeding usually begins in Batavia to become insufficient, as de Haas demonstrated some time ago, the body weight increasing less than in European infants about that time. Naturally this cannot be the only factor, because this method of feeding is common in the Indies, but perhaps it can facilitate it when other toxic instances occur. Possible poisoning of the children by the mode of living or dressing of the

Chinese must also be taken into account ; de Langen proved that the degeneration of the white matter in the cerebrum only occurring in Chinese children was caused by lead intoxication. Originally an endogenous racial factor was supposed to exist, but it proved to be the habit with Chinese inhabitants to use lead-containing toilet powder because of its greater covering power, while the natives use rice and the Europeans talcum powder.

In the present cases this cannot be the reason, because lead certainly was absent in one of them and the typical lead lines in the bones were absent in two cases, but manganese must still be taken in account. With adults it is known that manganese can bring about degeneration of the striatum, causing tremors and increased tone of the muscles.

Caravan, Cobb and Drinker (1934) describe such a case in a man, who at the age of fifty-four developed similar neurologic disturbances that diminished as soon as he stopped working with manganese. After his death at sixty-eight atrophy of the lenticular nucleus was found with degeneration of the neurons, but without disintegration of the tissue or proliferation of the neuroglia. Therefore the resemblance is not great and the probability that manganese has something to do with the cases here described is slight.

Endogenous racial factors can be considered for the differences between disease in the Indies and Europe probably do not wholly depend on exogenous causes. It is certain that multiple sclerosis and Huntington's chorea are much less frequent here than in Europe or America ; with Japanese this type of chorea has not yet been found and in the Indies only two cases have been described. With natives the great frequency of primary cancer and cirrhosis of the liver and the rarity of cancer of the stomach are remarkable facts that have not yet been altogether explained. Notwithstanding the frequency of cirrhosis of the liver, pseudosclerosis has not yet come to autopsy in natives although mild specific changes of the neuroglia in the striatum have been found frequently in cases of cirrhosis of the liver. Once only a patient suffering from the cirrhosis showed tremors and increased tone of the limbs for some weeks before death ; in the striatum neuroglial changes and mild degeneration of ganglion cells were present.

To sum up : at the moment it is impossible to express an opinion about the differences in pathology between races, but these cases are described as interesting contribution to the causation of degeneration of the striatum.

Postscript : I have only now become acquainted with the paper of A. Biemond and S. v. Creveld (1937), on nuclear jaundice in neonatal sepsis with jaundice. The post-mortem findings have something in common with those in the present cases, namely degeneration of the corpus subthalamicum and the pallidum, but the putamen is unaffected. Moreover, the clinical history showed great differences ; in their cases the infants were seriously ill shortly after birth with high fever and jaundice, they developed their neurological symptoms at that time and these symptoms remained unchanged until death occurred several months later. I therefore think that the cases here described cannot be of the same origin.

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CLINICAL ASCARIASIS IN CHILDREN

BY

CICELY D. WILLIAMS, D.M., M.R.C.P., D.T.M. & H.

The accounts of ascariasis in standard text-books appear to be inadequate to those who have had much practical acquaintance with the infestation.

Paterson (1937) states 'Children infected with ascaris appear in moderately good health.' In 'Diseases of Children' by Garrod, Batten, Thursfield and Paterson (1934), it is recorded that 'there are no clinical symptoms by which round worm can be diagnosed until the worm appears.'

The ascaris index of a population is an important indication of its sanitary advancement. In countries where ascariasis is prevalent, and in some places up to 70 per cent. of the population may be affected, it is necessary to appreciate the variety and the severity of the conditions which may be produced. It is true that many adults may harbour the worms without much obvious inconvenience. The discovery of their presence during routine examination in healthy individuals and also in hospital patients whose disease seemed to be in no way connected with the condition, has led to the firm and often dangerous belief that these parasites are almost harmless. Whatever may be the immunity developed or acquired by adults, it is certain that the health of children may be seriously undermined by these helminths, and their presence is responsible for a vast morbidity and a considerable mortality.

General Considerations

The ascaris seems to be practically world-wide in distribution. It is common in the north-east districts of London and nearer the equator it is much more common. It abounds more profusely where sanitation is primitive and where there is a low standard in matters of toilet. In a tropical climate, where children spend most of the day playing about the ground near houses, there is more chance of mass infection. Males and females are equally affected. The patients generally come from unhygienic homes, but even the most protected and carefully nurtured children may occasionally become victims. Infection may take place at any time after birth, probably from the dirty fingers of the mother or other attendant; sometimes also from the 'comforter' that is dropped about the floor. This article seems to appear with great persistence as one of the first harbingers of civilization in every unsanitated family.

At post-mortem examinations I have twice seen an ascaris four inches long in the stomachs of babies of four months who died with the symptoms of acute enteritis. Mass infestation is, however, rare before one to three years of age. At this stage a child learns to crawl about the ground, and is in the habit of putting, unchecked, dirty fingers, dirty food and all manner of stray objects into its mouth. The ground is shared by many other children, adults and animals, nearly all with insanitary habits. Heavy ascaris infestation is most common between two and six years old. After this age children may acquire some immunity. They become less inquisitive as to taste, more selective in appetite and therefore less likely to ingest objects that are grossly contaminated with faeces and hence with ascaris ova.

Routine examination of stools may lead to the discovery of the eggs at any time after six months of age. Occasionally even repeated examinations may yield entirely negative results, but the child may proceed to vomit or pass per rectum one or two well-grown ascaris. This is particularly apt to happen when there are only a few worms present, and these may be males. It would be useful if x-ray diagnosis could be perfected or if some more reliable cutaneous reaction could be employed, particularly in the case of small babies. At present there is no certain method of diagnosis except the discovery of ova in the stool.

Signs and symptoms

A well-marked case is so typical in appearance that the diagnosis is obvious, but the mild infestation may present great difficulties in diagnosis. The signs and symptoms depend on the age of the child and the degree of the infestation, and on whether the condition is acute or chronic. The classical signs, picking the nose and grinding the teeth, are frequently but not by any means invariably present. In a small baby the symptoms are generally those of enteritis or gastro-enteritis. The alimentary tract is more irritable than that of an older child and the worms are therefore more easily vomited or evacuated before the condition becomes chronic. The toxaemia may be severe. In an older child the symptoms may be vague and elusive. There may be mild attacks of toxaemia. Cyclical vomiting that defeats treatment may end with the appearance of one or two worms. In other cases the child fails to gain weight ; he is labelled as ' intestinal indigestion,' ' malnutrition ' and ' nutritional anaemia.' Anaemia is almost always present, the haemoglobin being generally decreased to 20–60 per cent., while the blood picture is that of a secondary anaemia with sometimes an accompanying eosinophilia. These children are also particularly subject to attacks of urticaria, asthma, bronchitis and pneumonia. Their pulmonary complaints may be due to some extent to the passage of larval forms through the lungs, and also to some toxic or allergic factors, as well as to the fact that they are exceedingly subject to intercurrent infections. Traces of albumin may be found in the urine, and it is probable that the presence of ascaris is connected with an increased incidence of pyelitis and nephritis. Many cases suffer from attacks of diarrhoea. In a chronic case the stools may contain material that is so undigested that the food is passed per rectum

practically unaltered in appearance and only slightly more offensive in smell. These attacks of diarrhoea may alternate with obstinate constipation. During these, aperients seemed to be almost powerless. There may be acute attacks of abdominal distension, simulating an acute obstruction. The abdominal musculature seems to be so weakened with distension that it refuses to act. In many of these cases it is found beneficial to encase the child in a firmly applied spiral corset of elastoplast. This seemed to reinforce the abdominal muscles and aids digestion as well as elimination.

A well-marked case of ascariasis presents a most typical appearance. The child is from two to five years old. He is peevish, with stolid intervals. He is pot-bellied and spindle-legged, with oedema of the face, hands and feet so well marked as to suggest a nephrosis. The hair is sparse, dry and staring. In an African child the hair loses its natural curl and becomes almost straight. The skin is dry and atrophic and is subject to sores and boils. A child that should be normally pigmented becomes much paler. In an African this depigmentation may be striking.

In some patients who presented the picture of typical and profound ascariasis it was found impossible to obtain any evidence of the presence of the worms. In these cases the child's condition was so feeble that probably the worms found but poor lodging and had been eliminated during an attack of diarrhoea. Many children are reduced to a pitiable condition and may die even after all the worms have been evacuated, as their intestines become so damaged and atrophic that they lose all power of assimilating nourishment.

Various observers quote enormous numbers of ascaris being passed by one individual. Between one and two hundred are not rare in children of about four years old. Sometimes the actual mass of worms reaches a surprising proportion of the total weight.

A child eighteen months old was admitted to the Children's Hospital, Accra, weighing 16 lb. After de-worming she weighed 12 lb. and subsequently proceeded to put on weight of a more desirable sort and made a good recovery.

Complications may be many and various. The worms may cause obstruction in the nose, appendix, intestines and gall bladder. At post mortem they may be found in the bile ducts throughout the liver, accompanied by multiple liver abscesses. They may even give rise to intestinal perforation and peritonitis.

It would seem that ascaris may eventually produce some sort of immunity, hence the fact that though a small child may be made ill by the presence of one worm, yet older children and adults may harbour many without obvious inconvenience. The immunity may be comparable with that produced by the tumbu fly. Babies and new-comers to the country may be infested with these larvae, but the adult native generally escapes.

Treatment

Of all the remedies, oil of chenopodium is the safest and most effective in children. It is unsuitable for out-patient administration. If the child cannot

FIG. 1.—Ascariasis in an African (Ashanti) child.

Depigmentation : hair (very short in this case) dry, sparse, straight, and staring ; pendulous cheeks, distension of abdomen and oedema of extremities. The child was four years old and weighed 18 lb. She died after two months in hospital. Both parents were full-blooded Africans.

FIG. 2.—Ascariasis in a Chinese child (Singapore).

Skin is a dry, earthy colour. Hair rather thin, dry, and with a reddish colour. Chinese hair is normally jet black. Oedema of cheeks and extremities and distension of abdomen is well shown, also the stolid outlook. Child made a good recovery, after producing nearly 200 ascaris.

(Photograph by permission of the *Straits Times*.)

be admitted, then santonin is undoubtedly a more suitable drug to be given at home. If, however, this has been unsatisfactory, the parents can be instructed to give aperients and a fluid diet at home ; the child is kept under observation in the hospital or dispensary for four to five hours while the chenopodium treatment is given. A fluid diet and sulphate of magnesia rather than any other aperient are important points in the treatment. The routine for an average child of three years old would be as follows :

1ST DAY : Fluid diet, with glucose ad lib.
Mist. Magnesium Sulphate. (60 grains to the ounce.) ¼ to ½ ounce. t.i.d.
2ND DAY : 6 a.m. Mist. Mag. Sulph. ½ ounce.
7 a.m. Ol. Chenopodium. 6 minims.
8 a.m. Ol. Chenopodium. 6 minims.
9 a.m. Mist. Mag. Sulph. ½ ounce.
Repeat Mist. Mag. Sulph., if bowels not open at least twice after last dose of chenopodium.
3RD DAY : Mist. Mag. Sulph. ½ ounce, twice a day.

It is important to ensure that the bowels are well opened after the last dose of chenopodium. If the nursing staff observes these directions strictly large doses of chenopodium can be employed to evacuate the worms without danger of toxic effects on the child.

If the child is admitted acutely ill, it is generally better to postpone deworming until the condition is improved by general measures, or to start the treatment with a tentative dose of santonin.

When the question of immunity has been investigated it may be that some method of artificial immunization may be discovered that will prove valuable in counteracting the severe forms of toxaemia that are met with, especially in young children.

Prevention

The first step in prevention is the education of the parents. They must be taught to regard helminthiasis as a preventable disease and a worm-infested child as a disgrace—which indeed it is. Young babies should never be handled by anyone whose hands are dirty. As soon as the baby begins to crawl, he should be provided with a play pen and a mat which can be cleaned easily. Children should be taught from the earliest age not to put anything except clean food into their mouths. They must be taught to defaecate into a pot, commode or latrine, never on to the ground. The Matron, Rural Health Department, Singapore, suggests that when the parents are too poor even to provide a pot, the children can be taught to use a large leaf which is afterwards removed and buried. Children must be taught always to wash their hands before meals and after defaecation. All compounds should be provided with adequate latrines, but it must be remembered that material structures are practically useless unless they are accompanied by health education.

Summary

(1) Ascariasis causes a vast morbidity and considerable mortality in children, especially in unhygienic conditions and in the tropics.

(2) The symptoms may include enteritis, gastro-enteritis, asthma, bronchitis, pneumonia, anaemia, oedema, nephrosis and malnutrition. They may simulate an acute abdominal emergency.

(3) Oil of chenopodium is probably the safest and most effective form of treatment.

(4) Health education is the most effective method of prevention.

I have to thank the Director of Medical Services, Malaya, for permission to publish this article.

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PRECOCIOUS PUBERTY WITH A REPORT ON A CASE OF PINEAL SYNDROME

BY

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The awakening of sexual maturity is an event of considerable physiological interest, and in the light of modern knowledge of the endocrine mechanisms a profound series of hormonal reactions is known to occur. Clinical observations have gradually brought to light some of the integrating factors involved in this epochal development ; and by the careful study of aberrations from the normal, principally in cases of delayed or in accelerated puberty, it is now possible to state with some accuracy a single cause or a group of causes. It is now generally recognized that the pituitary is normally the primary directing power behind sex development, although there are most important second stations within the adrenal cortex and gonadal interstitial cells. The failure of sexual development is usually a selective or composite pituitary anterior lobe deficiency, and recent observation in pituitary cachexia has indicated the case whereby the whole endocrine basis may fail and sexual repression occur when the anterior pituitary is atrophic.

Clinicians have recognized remarkable aberrations of physical and sexual development accompanying certain types of disease within the nervous system, and in this respect the region of the midbrain and especially the immediate neighbourhood of the floor of the third ventricle is principally concerned. It would appear from a study of case records that the hypothalamic area bears some close integration in function with the pituitary gland in regard to both lobes.

Cloake (1927) reports a detailed study of the anatomy of the hypothalamic area, and he notes the vast number of small cells of unknown functions in the tuber and the fact that the pituitary gland receives nerve fibres from this region. Experimental evidence is extensively surveyed and no doubt is placed upon the vital functions of the tuber and neighbouring nuclei in their physiological rôle in carbohydrate, water, and body weight regulation. Collateral function with the pituitary and the sympathetic mechanisms is adduced and even psychic changes have been observed in syndromes of tuberal origin. This author sums up his views, after a most careful anatomical, physiological and clinical survey —' the posterior lobe is but a displaced part of the tuber, and its displacement so far back in the scale of evolution would seem to point to a close functional relation between it and the anterior lobe and pars intermedia and with the region of the brain whence it was derived.'

Disorders, especially polyuria and obesity, referable to posterior lobe dysfunction following inflammatory disease in midbrain centres are discussed in detail by Eaves (1930). Walsh (1926) observed a general tendency to change in physical stature after mesencephalic encephalitis. Similar phenomena are occasionally seen after prolonged chorea.

An interesting clinical story is related by Stewart (1938). A male child, aged three, acquired obesity, which was followed later by polyuria, polydipsia, excessive somnolence and finally hyperglycaemia. Microscopically gliosis and chronic degenerative changes were found in nerve cells of the hypothalamic nuclei.

Schlesinger (1934) records the case of a girl aged eight-and-a-half years, who developed precocious sexual appearances following postbasic meningitis with internal hydrocephalus. Ford and Guild (1937) review precocious puberty in the light of nervous disease and record two cases of premature sexual development in young girls after measles-encephalitis and in one boy after encephalitis lethargica.

Neoplastic processes arising in the hypothalamic tissue have been associated with the development of considerable sexual precocity. An example is recorded by Heuyer (1931) in a boy aged six years. Macrogenitosomia and advanced secondary sexual character developed. Pathological investigation later revealed an ependymoglioma in the region of the infundibulo-mammillary zone, strictly limited in nature and without any destructive effects upon the hypothalamic centres. Dods (1934) observed a boy aged three years to be precociously developed and by the age of eight years showed the sexual characteristics of late adolescence. An astrocytoma of the floor of the third ventricle was present. Probably the most remarkable example recorded to date concerning this group syndrome is that of Marchard and Russell (1935). In this case pubertas praecox was associated with a tumour of the floor of the third ventricle. At the age of two years considerable sexual excitement and at times almost maniacal activity was observed. His mental and physical development was amazingly precocious, and the authors acted heroically in an attempt to stem the rush of his sexual behaviour. One testicle and later one suprarenal gland were removed without any improvement. There were no neurological physical signs indicative of an intracranial lesion, but in retrospect the authors regard the facts of subnormal temperature, extreme variations in behaviour and restlessness to be of localizing value and might have directed suspicion upon the subthalamic areas. The exaggerated activity and abnormal sexual behaviour seen in this case were similar to those seen in some cases of post-encephalitic psychosis. It should be mentioned, in contrast, that the central characters in this case were rather contrary to the more usual reserved and quiet character of many children with precocious puberty. Reserve, possibly due to a degree of selfconsciousness, is rather a feature of macrogenitosomia. This boy died of acute rheumatic carditis at the age of four-and-a-half years. Necropsy revealed no detectable intrinsic endocrine abnormality. The pituitary and the pineal glands were normal. A circumscribed tumour was found attached to the right corpus mammillare and to the left side of the tuber cinereum. There was no hydrocephalus and no obvious disturbance of the adjacent hypothalamus, apart from slight pocketing of the floor of the third ventricle where the tumour was attached. In a general review these authors advance the hypothesis that in cases in which the pineal, the adrenal, the gonads, or the hypothalamus are involved, pubertas praecox may occur by an influence on the hypothalamic centres and from these on the pituitary.

It is a remarkable fact that in no case of sexual precocity has a tumour or a directly responsible lesion in the pituitary gland been detected (Lisser). This is

in contrast with the interesting clinical appearances brought about in hyperplastic or neoplastic changes in other endocrine glands. The suprarenal cortex, especially when tumour formation is present, leads to masculinization, heavy somatic development and sexual precocity. Brilliant results are therapeutically possible in such patients, as for instance in Lisser's case of an adrenal cortical adenoma removed by operation in a boy aged five years, who had remarkable sexual virilism, but was freed from this by the surgical success. Masculinizing influences are seen in the more rarely occurring ovarian arrhenoblastomas. Precocious puberty and menstruation, but not necessarily ovulation, is a rare occurrence in girls, but examples of this disturbance are now amply recorded, and the significantly associated granulosa cell ovarian tumour has become an established clinical entity. By analogy the true interstitial-cell tumour of the testicle, inducing early sex development, is recognized and a typical case is recorded by Sutherland (1932).

The pineal gland would seem to be a physiologically inactive body. Experimental investigation has yielded negative results. Quite recently a further amount of work has been done on pineal tissue, a large amount of which has been available; detailed examination has so far failed to demonstrate any hormonal activity on mammals (*Med. Res. Council Report*, 1936–1937). Information to date seems to indicate that the pineal body plays no significant rôle in the production of macrogenitosomia praecox, the gland having been found to be normal in many cases of the fully-developed syndrome, and destruction of the pineal has not led to any apparent change in the genital organs. There is no instance where a verified true pinealoma has been found in macrogenitosomia praecox (Ford and Guild). However, a tumour of the pineal area and of the hypothalamus may produce a similar syndrome.

Gardiner-Hill (1937) reviews the general situation and observes that the 'pineal' tumours found in cases of macrogenitosomia praecox have only one feature in common—that they arise in the general region of the pineal. It would appear that the pineal played no intrinsic significant part in the production of the general body changes and that the syndrome is probably due to a direct or indirect destructive process in the walls of the third ventricle. Gardiner-Hill regards the clinical picture, apart from the neurological signs, as quite similar to that of macrogenitosomia praecox due to interstitial-celled testicular tumour. Confusion and difficulty surround possible explanations why a tumour in the pineal zone may produce signs of sexual precocity, and it must remain for the present a simple clinical fact that male children only are affected in this way.

Kinnier-Wilson (1925) observed that pubertas praecox was more often not seen than seen in these tumours, and he questioned how much was due to neighbourhood disturbances. It would appear that occasionally a 'pineal' tumour may be associated with sexual involution, as is reported by Cleghorn (1938) of a male aged twenty-three years, who had a tumour ('pinealoma') causing internal hydrocephalus, hypogonadism and some evidence of other endocrine insufficiency. He proposed that the condition had been brought about by neuropituitary disturbance, there being, however, no histological abnormality in the pituitary gland.

The first review of pineal tumours was made by Horrax and Bailey (1925). They regard the pineal gland to be composed of two categories of cells : (*a*)

parenchymatous and questionably glandular, (*b*) neurological ; and that neoplasia may involve either cell type, but no correlation with sex-stimulating effect could be ascribed to either. Of twelve verified cases five occurred before puberty and seven in adults. The girls affected showed no sexual precocity. Haldeman (1927), in a survey of 113 cases of pineal tumour, found that fifty-three had occurred in persons under twenty years of age, and of these forty-five were males and eight females. In the male cases sixteen, all between the ages of three years and twelve years, showed macrogenitosomia praecox, and in ten the pathology of the tumours was histologically teratomatous.

Owing to the anatomical locality of the pineal tumour it is clear that the neurological effects chiefly concern the oculomotor apparatus, the inferior corpora quadrigemina, the cerebellum and cerebellar peduncles, with superimposed signs due to intracranial pressure, and internal hydrocephalus. Horrax (1925) states ' in the presence of an intracranial pressure syndrome which simulates a cerebellar lesion, if there be added to the picture an involvement of one or both trochlear nerves, together with recurring changes in the size of one or both pupils and a tendency to spasticity in the lower limbs, a tumour of the pineal body should be suspected.'

Kinnier-Wilson observed that tumours in the antero-posterior axis of the brain tend to cause falling in backwards or forwards directions, and that pineal tumours had a special tendency to set back upon the superior corpora quadrigemina and be associated with loss of up-and-down movements of the eyes. Haldeman, in his large series of cases, found significant localizing signs to be paralysis of upward eye movements, diplopia, trochlear palsy, ptosis, nystagmus, and occasionally absence of the light reflex of the pupil.

Within the clinical experience of any individual physician or even in that of a large hospital, the occasion for recognition of the pineal syndrome with pubertas praecox must be very uncommon ; yet the clinical picture is so remarkable and characteristic, and, as the present case shows, remedial therapy may prove so promising and dramatic in effect, that the writer considers it of importance that clinicians should recognize the disorder and institute as early as possible therapeutic measures, principally to check the papilloedema and to minimize the precocious sexual changes.

Case Report

Eric K, aged nine years, was the first child of three. The boy seemed perfectly well until August, 1936, when he began to vomit. This, in the early stages of the illness, usually occurred early in the morning ; but as time went on he vomited several times a day. It was some months later (December, 1936) that he developed frontal headache. Each attack was severe and lasted about thirty minutes. During the following two months a gradual impairment of his sight took place, this being first recognized at school owing to his increasing difficulty in seeing the blackboard. He developed secondary sexual characters during the six months before coming under medical observation in March, 1937. The boy had not shown any mental changes or sexual advancement and his parents were not particularly concerned about him beyond the troublesome vomiting.

Clinical examination showed him to be a big, well-developed child with

strong muscles, heavy and bushy eyebrows, hair on the upper lip, abundant pubic hair, and the external genitals were of adult type. The testicles appeared normal, but proportionately enlarged. Thoracic and abdominal examinations were negative. No suprarenal gland abnormality was detectable; thyroid gland was normal. Heart and blood vessels were normal. Blood pressure was 120/70 mm. Hg. Urine and blood were normal. Ophthalmoscopic examina-

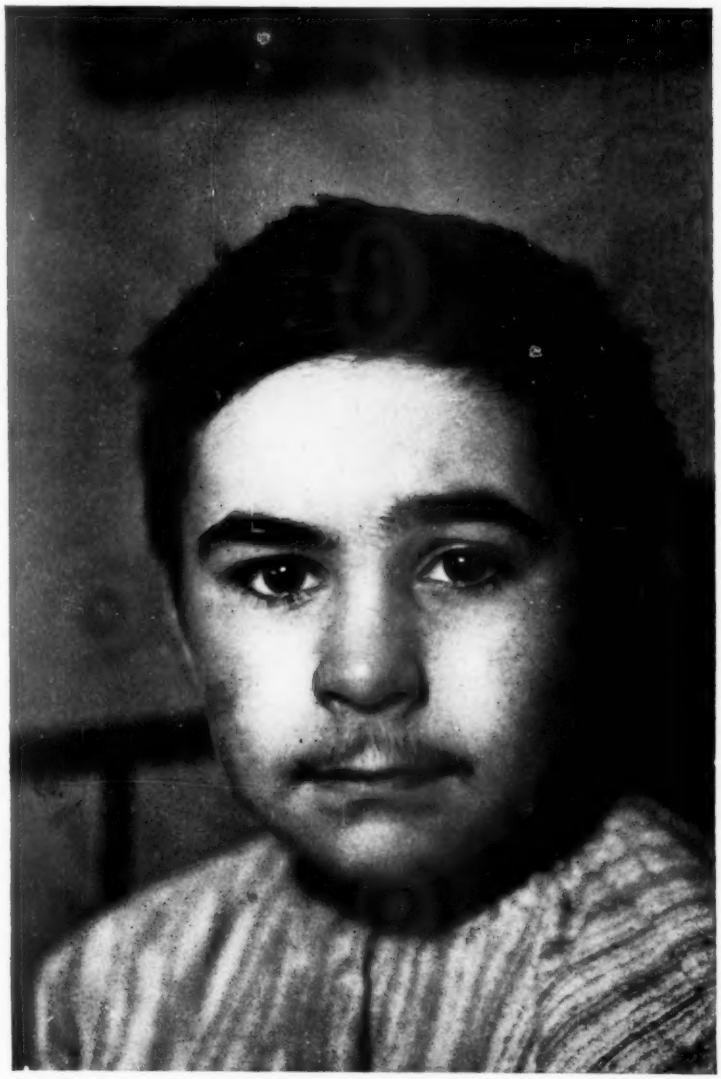

FIG. 1.—Eric K.

tion revealed bilateral and severe papilloedema. There was slight spasticity of the lower limbs. The left plantar reflex was extensor. Right plantar reflex was variable. There was nystagmus chiefly on left deviation and slight on right deviation. Ocular movements were full. There was no loss of vertical movement of the eyes. The pupil reactions were normal. The visual fields showed general contraction and did not suggest direct pressure in the visual pathways, but some general and indirect pressure, possibly by enlargement of the third ventricle (Dr. P. Jameson Evans). The cerebro-spinal fluid was clear and

normal. Ventriculography (Mr. Stammers) showed that the lateral ventricles and the third ventricle were enlarged. The ventricular system filled with air as far as the aqueduct of Sylvius. A block was present at this level and no air filling occurred in the fourth ventricle. This evidence confirmed the localization of the tumour to be at or near the pineal zone.

FIG. 2.—Eric K and a boy of the same age.

TREATMENT.—In consultation with Mr. Stammers it was decided that direct exploration of the tumour was highly dangerous, and therefore deep x-ray treatment was decided upon. A right temporal decompression was carried out as a preliminary measure. Fourteen days later deep x-ray therapy was commenced by Dr. Bromley at the General Hospital. This therapy consisted of twenty-one treatments to three fields—2,100 V. units to skin by each field and 2,900 V. units to the tumour. This treatment was concluded in July, 1937. During the treatment there was a variable degree of intracranial pressure, as

judged by the tension in the decompression area, and on several occasions considerable increase was evident and associated with severe vomiting ; but these symptoms were controlled by intravenous hypertonic glucose solution. In a few weeks remarkable improvement was evident, the neurological signs had disappeared, vision improved, and there was a marked decrease in papilloedema.

FIG. 3.—Ventriculogram showing dilated ventricles.

In November his condition was satisfactory, but there was no appreciable change in the sexual organs. In May, 1938, his height was 4 feet 9 inches and he weighed seven stone ; he had good vision, the visual fields were practically full and the fundi clear. He had returned to school.

The causation of sexual precocity in ' pineal ' tumours remains a physiological mystery, but the puzzle may be solved when the functions of the midbrain are better understood and more information on neuro-endocrine linkage is available.

In this case, which is the only example in which deep x-ray treatment is recorded, therapeutic success has occurred beyond expectation.

Thanks are due to Dr. Teall and to Dr. Thorpe for the radiographic examinations.

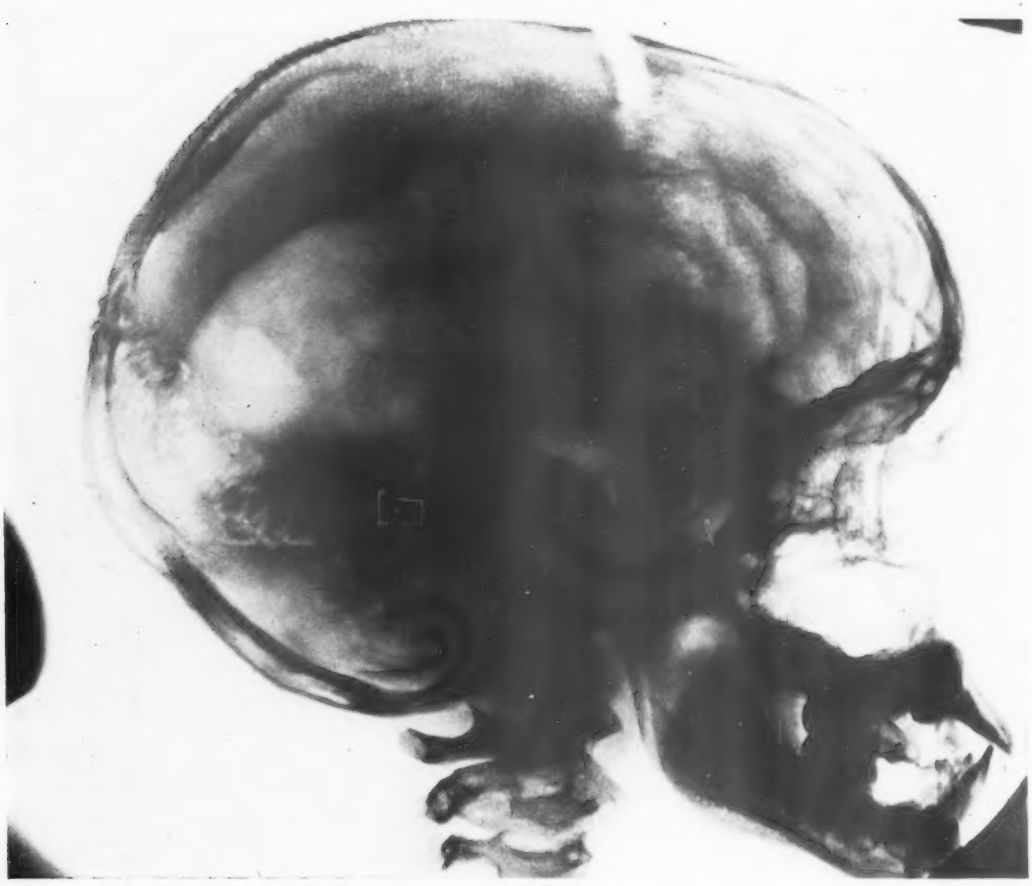

FIG. 4.—Ventriculogram showing obstruction at the aqueduct of Sylvius.

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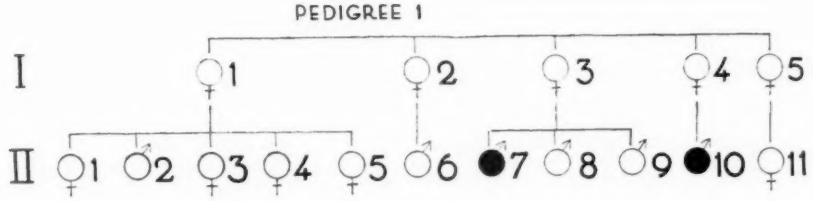
CONGENITAL PYLORIC STENOSIS IN FIRST AND SECOND COUSINS

BY

E. A. COCKAYNE, D.M., F.R.C.P.

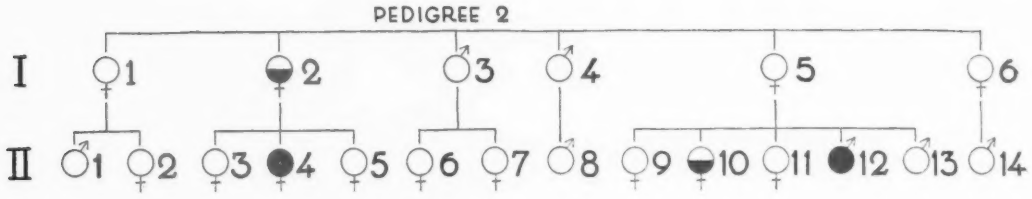
In 1934 I published two pedigrees of congenital pyloric stenosis in first cousins, and now I present three more of the same kind and a fourth in which the affected children were second cousins.



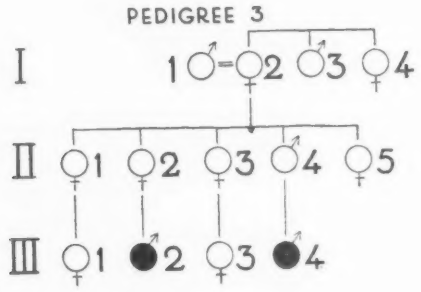
Case Records

Pedigree 1.—T. M., a male, aged five years, was admitted to the Hospital for Sick Children five years ago under the care of Dr. R. S. Frew with projectile vomiting and constipation. He had visible peristalsis and a tumour was felt. He was operated on at the age of five weeks on December 26, 1932, the diagnosis was confirmed, and he recovered. His first cousin, A. P., was admitted under the care of Dr. D. Paterson with similar symptoms, and the diagnosis of pyloric stenosis was confirmed at operation on September 14, 1937. He also recovered. I am indebted to the father of A. P. for the care he took in completing the pedigree.

I.1, female, aged forty-one, has five normal children born in the following order, a daughter, a son, and three daughters, aged respectively, seventeen, sixteen, fourteen, twelve and six years ; II. 1, 2, 3, 4, and 5. I.2, female, aged thirty-two, has one normal son, aged seven years, II.6. I.3, female, aged thirty, has three sons, the eldest, T. M., II.7, aged five, who had pyloric stenosis, and two younger ones, aged three and one-and-a-half, II.8 and 9, who are normal. I.4, female, aged twenty-eight, has one son, A. P., II.10, who had pyloric stenosis. I.5, female, aged twenty-four, has one daughter, aged two years, II.11, who is normal. Neither marriage which produced offspring with pyloric stenosis was consanguineous, and no other cases are known to have occurred in the family.



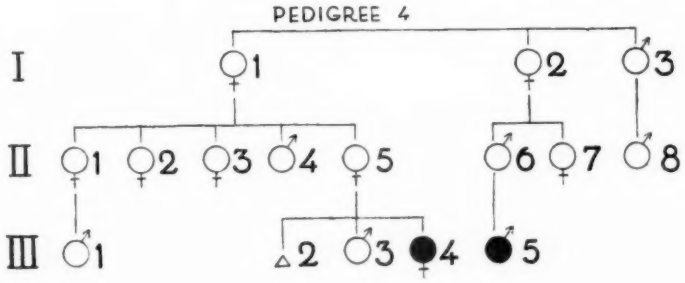
Pedigree 2.—For this pedigree I am indebted to Dr. R. R. Lane of Bolsover, who took great trouble to make it full and accurate. The ages are correct for November, 1937. I.1, female, aged forty-nine, has a son, II.1, aged twenty-two, and a daughter, II.2, aged ten both normal. I.2, female, aged forty-seven, as an infant had vomiting and constipation attributed to pylorospasm, and recovered with medical treatment. She had three daughters, the eldest, II.3, and the youngest, II.5, were normal, but the middle one, II.4, had pyloric stenosis verified at operation and died. I.3, male, aged forty-five, has two daughters, II.6 and 7, aged sixteen and fourteen, both normal. I.4, male, aged forty-three, had a son, II.8, who died at the age of four days. I.5, female, aged thirty-nine, has a normal daughter, II.9, aged ten ; a daughter, II.10, aged seven, who in the first weeks of life had vomiting, constipation, and loss of weight, diagnosed as pylorospasm, and recovered with medical treatment ; a normal daughter, II.11, aged six ; a son, II.12, aged four who had pyloric stenosis, confirmed at operation, and recovered ; and a son, II.13, aged two years, who is normal. I.6, female, aged thirty-six, has a normal son, II.14, aged nine years. Neither marriage which gave rise to a child with pyloric stenosis was consanguineous. It is interesting that the mother of the girl with pyloric stenosis and a sister of the boy with pyloric stenosis, her first cousin, both had an illness in babyhood which was diagnosed as pylorospasm. It is possible that this was a mild form of the disorder or at least a manifestation of the same gene.



Pedigree 3.—A. M., a male, aged two months, admitted to the Hospital for Sick Children under my care in June, 1937, suffered from vomiting and constipation and had visible peristalsis and a palpable tumour. The diagnosis of pyloric stenosis was confirmed at the operation and he was discharged on June 17, but was readmitted later with gastro-enteritis and died on July 18.

His first cousin, a boy, suffered from vomiting at the age of six weeks and shortly afterwards died from pneumonia with convulsions. His symptoms are said to have been like those of A. M. and his doctor told the parents that he had an obstruction in his stomach. Owing to the attack of pneumonia no operation could be performed and the diagnosis was not fully confirmed, but there can be little doubt that it was correct.

The grandparents are said to have been normal and the grandmother, I.2, had a brother and sister, I.3 and 4, both normal and both unmarried. II.1, female, aged thirty-six, has one child, III.1, a normal daughter. II.2, female, aged twenty-seven, has a son, III.2, the patient A. M. II.3, female, has one child, III.3, a normal daughter. II.4, male, had only one child, III.4, who died probably from pyloric stenosis. II.5, female, aged nineteen, is unmarried.



Pedigree 4.—M. E. S., a female born in 1934, was admitted to the Hospital for Sick Children under the care of Dr. R. S. Frew with vomiting, constipation, and visible peristalsis. The diagnosis of pyloric stenosis was verified at operation, and she recovered. H. L., her second cousin, a male, born in September, 1933, was operated on for pyloric stenosis and died at the age of six weeks. The diagnosis was confirmed, The father of M. E. S. took considerable trouble to compile a complete and accurate pedigree of his near relations.

I.1, female, has five children, all normal, three daughters, II.1, 2, and 3, a son, II.4, and a daughter, II.5. The eldest has one son, III.1, born in 1921, who is normal. The second and third are unmarried. The fourth, a male born in 1901, died at the age of thirteen weeks, but not from pyloric stenosis. The fifth, II.5, has had three pregnancies. The first ended in a miscarriage. The first living child, III.3, born in 1932, is normal, and the second, M. E. S., III.4, a girl, had pyloric stenosis. I.2, female, has two children. The elder, H. J. L., II.6, had only one child, the boy, R. L., III.5, who died of pyloric stenosis. The younger, II.7, who married in July, 1934, has no children. I.3, male, has only one child, II.8, a normal son.

Neither marriage which produced a child with pyloric stenosis was consanguineous, and no other cases are known to have occurred in the family.

Discussion

The etiology of congenital pyloric stenosis is still a matter in dispute, but there can be no doubt that heredity plays a most important part, if it is not the sole factor concerned. Many examples of its incidence in two or even three members of the same fraternity have been published and collected by Halbertsma (1935) and others, and there are several records of its occurrence in both members of a pair of monozygotic twins, collected by Sheldon (1938). The exact mode of inheritance is, however, still uncertain.

The great excess of males with the condition suggests that a sex-linked gene, recessive or incompletely dominant, is concerned, though the family histories

make it unlikely that it is determined solely by a sex-linked gene. The pedigrees published previously (Cockayne, 1934) and in this paper prove that it cannot be determined by a sex-linked gene acting alone. No such gene can be transmitted from father to son, because the X-chromosome of the male in man goes to his daughters, and only the Y-chromosome goes to his sons. Pedigrees in which first and second cousins have the condition are the best means of discovering whether a male can transmit pyloric stenosis to his son, because one may reasonably assume that when two sibs have children or grandchildren with the condition, they are the transmitters. Pyloric stenosis is not uncommon and coincidence might account for occasional instances in which the unrelated parent transmitted it to one of the affected cousins, but such cases would be rare in comparison with the others.

In these six pedigrees there are three instances of a man transmitting pyloric stenosis to his son. The pedigree published by Halbertsma affords a fourth instance and so increases the evidence against its determination by a single sex-linked gene.

In this interesting pedigree the grandparents were both normal, but they had a son with pyloric stenosis and a son and a daughter who were apparently normal. Of these two normal children the daughter had two sons with pyloric stenosis and a normal son, while the son had a daughter with pyloric stenosis, a normal son and a son with pyloric stenosis. Thus two boys with the condition in the one fraternity were first cousins to a boy and girl with it in the other fraternity, and there can be no doubt that an apparently normal man transmitted the condition to his son.

These pedigrees, however, do not prove that the condition is not determined by two independent genes, one sex-linked and the other autosomal. If this is the case the figures agree better with a dominant than a recessive autosomal gene. There are only one or two known cases of direct transmission of the condition from parent to child, and ignoring these the ratio of males to females with pyloric stenosis would be 5 : 1, assuming it to be determined by a recessive sex-linked gene and an autosomal dominant, and transmission of the sex-linked gene would be through the female alone in ten and through both parents in two of the twelve possible matings. The ratio of males to females with pyloric stenosis is at least 5 : 1 and agrees well with that expected on this hypothesis, and the ratio of female transmitters to male transmitters is 11 : 3 or with Halbertsma's pedigree 12 : 4 instead of the expected 10 : 2. There are, however, difficulties in the way of accepting this hypothesis, such as the rarity of consanguineous marriages and the low ratio of affected to normal children in the fraternities, apart from the fact that determination by two genes is less likely than determination by one.

An incompletely dominant gene with partial sex-limitation to the male would give results very like those actually found. It is clear that the mode of inheritance of congenital pyloric stenosis still awaits an explanation, but a large collection of pedigrees of the kind published in this paper would afford great help in solving this difficult problem.

Summary

(1) Four new pedigrees illustrating the occurrence of congenital pyloric stenosis in first and second cousins are published.

(2) In these four pedigrees, the two published in 1934, and Halbertsma's there are four instances of a man transmitting pyloric stenosis to his son.

(3) This proves that the condition is not determined by a single sex-linked gene, recessive or incompletely dominant, but does not exclude the possibility that it is determined by a sex-linked gene acting with an autosomal dominant gene.

Thanks are due to Dr. R. Frew and Dr. D. Paterson for permission to publish their cases.

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NUTRITIONAL OEDEMA IN CHILDREN IN EGYPT

BY

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A. A. EL GHOLMY, M.D.

(From the Paediatric Department of the Faculty of Medicine, Cairo.)

Oedema developing in the course of gastro-intestinal disorders of infancy has been noted in America by Maver (1920) and in Egypt by Shawki. It was of the same character as that which developed in adults during times of war and famine, as in Poland during the Great War, when the food available was of low caloric value (1200–1400 cal. per day) and no meat was obtained for months. The oedema, though resembling that of kidney disease, was not associated with any renal damage. Eighteen cases of gastro-intestinal disorder with oedema have been collected. All had previously been submitted to a prolonged period of starvation on medical or lay advice before attending the hospital because of some gastro-intestinal trouble and a variable fever. Food had been restricted to anisi or karaway and boiled barley or rice water. After a period varying from three days to two months, with an average of three weeks, during which the patients lost considerable weight and became pale and flabby, oedema appeared first in the eyelids, then in the hands and legs and lastly in the peritoneal cavity as ascites. No cardiac or renal disease was found to account for the oedema. The blood and oedema fluid of these cases were examined for their protein, chlorides, cholesterol and calcium content and the blood picture noted. The results are shown in the table.

The table shows certain features which will be dealt with more in detail later. In all except three cases the total serum protein was 4·5 per cent. or less, reaching the ' critical level ' as in experimental oedema (Weech, Snelling and Goettsch, 1933). The reduction was mostly in the albumin fraction. The chlorides, instead of being only 50 mgm. per cent. higher in the cellular spaces, showed an increase of at least 120 mgm. per cent. and reached as much as 482 mgm. per cent. difference between the blood and oedema fluids in one of the cases. All cases showed a severe hypochromic anaemia with a low reticulocyte count. The cholesterol content of the blood was always low. The anaemia and general weakness tended to persist after the oedema had disappeared. From the table two facts stand out : (1) the almost constantly present hypo-proteinaemia ; and (2) the increased chloride content of the oedema fluid.

		BLOOD					OEDEMA FLUID				
CASE NO.	AGE, YEARS	PLASMA, TOTAL PROT., PER CENT.	ALB., PER CENT.	GLOB., PER CENT.	CHOLESTEROL, MGM. PER CENT.	CHLORIDES, MGM. PER CENT.	TOTAL PROT., PER CENT.	ALB., PER CENT.	GLOB., PER CENT.	CHLORIDES, MGM. PER CENT.	TIME AFTER WHICH OEDEMA APPEARED, IN DAYS
1	2	3·6	2·1	1·35	98	468	1·2	0·85	0·3	643	10
2	3	3	1·8	1	145	468	1·4	0·8	0·6	655	15
3	2	2·45	1·4	0·9	55	526	0·8	0·6	0·2	838	30
4	3	3·45	1·45	1·8	127	468	0·87	0·72	0·15	672	10
5	2	4·9	2·7	1·85	105	526	1·1	0·9	0·2	958	30
6	$2\frac{1}{2}$	2·75	1·2	1·3	125	409	0·3	0·3	—	672	15
7	2	4·05	2·2	1·55	45	468	0·29	0·29	—	760	60
8	2	4·5	2·9	1·4	80	585	0·5	0·5	0·18	597	10
9	2	3·2	1·65	1·3	115	409	0·8	0·8	0·1	760	3
10	8	3	1·6	1·2	130	375	1·42	1·42	1·32	770	21
11	2	4·4	2·3	1·75	85	448	0·4	0·4	0·1	789	20
12	2	3·3	1·27	1·75	136	450	0·31	0·31	0·09	760	21
13	2	4·3	2·1	1·85	85	468	0·17	0·17	0·05	772	27
14	10	4·2	2	1·9	100	452	0·15	0·15	0·03	740	15
15	$1\frac{1}{2}$	4·2	2·8	1·25	107	585	0·16	0·16	—	819	30
16	$2\frac{1}{2}$	5·2	3	1·95	125	468	0·4	0·4	0·05	807	4
17	3	4·6	2·8	1·65	117	540	0·3	0·3	—	600	7
18	2	6	3·7	2·1	95	585	0·75	0·75	0·3	736	30

The calcium estimations were all within normal limits and about 2 per cent. lower in the oedema fluid.

Comments

Oedema develops whenever the rate of passage of fluid from the capillaries into the tissue spaces exceeds the rate of its absorption by the lymphatics. This occurs when there is :

(1) Lowered effective colloid osmotic pressure of the plasma, i.e. when the colloid osmotic pressure of the plasma becomes less than that of the cellular fluid ;

(2) increased permeability of capillary endothelium to salt and water ; and

(3) abnormal mechanical forces.

1. Since a solution containing 9 gm. of sodium chloride per litre is isotonic with the blood serum it follows that the serum chlorides (which are present to the extent of 4·5 to 5·5 gm. per litre of blood) contributes about two-thirds of the osmotic pressure of the blood. The remaining one-third is contributed by the bicarbonate and the proteins in the proportion of 3 to 2. Though oedema fluid and transudates are in approximate diffusion equilibrium with blood plasma, the chloride concentrations in the former are a few per cent. higher. The lower chloride content of the plasma is compensated for by its higher protein concentration. This balance of osmotic forces is liable to variations, due either to the diminution of plasma protein inside the capillaries or to its increase in the tissue spaces as in cases of cardiac failure (Smith, 1937) or to local inflammation. Although the plasma crystalloids have a much higher osmotic value (5,000–6,000 mm. of mercury) than that of proteins (30 mm. of mercury), yet these crystalloids are of little primary influence upon the fluid distribution, as they can easily pass through capillaries. The normal tendency of diffusion in capillaries were the proteins to be diminished or absent would be for the water to pass out under the influence of blood pressure. The restraining influence of the oncotic pressure of the plasma proteins is essential for the normal distribution of fluids in the body. The marked effect of the plasma protein upon the distribution of fluids in the body has been well shown by Weech, Goettsch and Reeves (1935) on dogs. They proved that in feeding dogs on protein-poor diets they could reduce the serum albumin (Weech and Liny, 1931) (serum globulin is not similarly affected) and produce oedema. Though tissue metabolism helps to limit this protein loss in dogs and man (Lin, Chu, Wany and Chung, 1932), yet on prolonged feeding from one to three months on such a diet the plasma albumin could be reduced to the critical level of oedema formation. They also showed that during recovery by feeding on protein-adequate diets if no marked weakness and loss of vitality had occurred, the rise in serum albumin can be rapid. When the experiment was prolonged to a critical point with marked weakness and severe anorexia, recovery was much more tedious, and careful feeding by gavage on milk and casein, lean meat or liver, and stimulating the appetite by feeding on bread and vegetables were found necessary. A rise of serum protein was usually obtained, in some slowly, in others more rapidly, but not always associated with improvement in the general condition. The same authors also showed that prolonged protein deprivation in dogs produced histological and symptomatic evidence of liver

damage. It is thus possible that return of serum protein to normal levels is determined not only by adequate diet but also by the time required to restore physiological normality of the liver and other tissues concerned with protein synthesis.

The lowered effective osmotic pressure of the plasma in the investigated cases is evident from the table published above in the marked degree of hypoproteinaemia. It was also noticed in this series of cases, as in the dog experiments mentioned above, that though the oedema disappeared within one or two weeks, yet improvement in appetite and blood picture was slow. Enlargement of the liver with marked pallor and cellular changes were seen post mortem in some of the cases.

2. The increased permeability of the capillary endothelium to salt and water is shown in the marked increase of oedema fluid chlorides. These are normally only about 50 mgm. per cent. higher in the tissue fluids than in the blood, but in the series of cases investigated the difference was always above 120 mgm. per cent. There was rarely any reduction in the serum chlorides, as patients usually received sufficient salts in their diets. In two cases (no. 9 and 16) oedema appeared rapidly in three and four days respectively. Though the duration of the gastro-intestinal disorder was short, yet the previous state of nutrition was poor and the imposed starvation due to the intestinal disease did not require a long time to tip the balance in favour of oedema.

3. Except for gravitation causing an increased local venous pressure, mechanical forces have little effect. Muscular movement lowers the local venous pressure considerably below the level at rest. Any illness reducing muscular activity will increase local venous stasis and pressure and help in the production of oedema.

Summary

Eighteen cases of gastro-intestinal disorder with oedema, of which three had also tuberculosis of chest and otitis media, were collected. They all showed on investigation a marked hypochromic anaemia, hypoproteinaemia, lowered cholesterol in the blood and a rise in the chloride content of the oedema fluid. This picture is similar to the starvation oedema of animal experiment. The prolonged starvation produces profound metabolic change associated with marked hypoproteinaemia and chloride retention in the tissues. Marked liver damage is often noticed post mortem, suggesting that the rôle it plays in the protein metabolism may be also disturbed.

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SPONTANEOUS SUBARACHNOID HAEMORRHAGE IN CHILDREN

A CLINICAL STUDY OF FIVE CASES

BY

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The modern literature of subarachnoid haemorrhage may be said to begin with a classical paper by C. P. Symonds (1924), in which he describes the syndrome of haemorrhage into the subarachnoid space occurring spontaneously and apart from any injury or recognizable disease, and frequently traceable to a ruptured congenital aneurysm of the circle of Willis or one of its branches. Here is found correlated for the first time the subarachnoid haemorrhage of earlier writers (Gintrac, 1869 ; Hayem, 1872 ; Froin, 1904), with the detailed anatomical observations of Fearnsides (1916) on intracranial aneurysm. Since then several authors have amplified Symonds's work. Nattrass (1933) describes the various clinical pictures produced by bleeding from aneurysms of this nature ; and Taylor and Whitfield (1936) analyse eighty-one cases occurring in Birmingham, and make valuable observations on incidence, mortality, symptomatology and pathology.

References to the occurrence of spontaneous subarachnoid haemorrhage in children are few. In the general literature of the condition Nattrass (1933) comments on the apparent rarity of the syndrome in childhood, and one case in a child of ten is included in Taylor and Whitfield's series. Apart from these there are some isolated case reports of the condition occurring secondarily to other pathology. Thus Gintrac (1869) reports a case in a child of eighteen months secondary to superior longitudinal sinus thrombosis ; between this time and the present day the French in particular have developed an extensive literature on the subject, of which an article by Traissac (1937) may be taken as representative. In a long paper on the subject he describes subarachnoid haemorrhage occurring in association with practically every disease that afflicts the child—infective fevers, blood diseases, tuberculosis, rheumatism and ' méningite lymphocytaire curable ' ; and attributes those cases which he recognizes to occur in children otherwise healthy to a haemorrhagic meningitis. This hypothesis is put forward in view of the absence of arteriosclerosis, atheroma and syphilis as causative factors in those children, and in apparent ignorance of the English work on intracranial aneurysm. He also propounds the theory that prognosis in these cases depends on the virulence of the activating and unrecognized infective agent.

The first reference to the condition occurring in children in the absence of other disease appears to be Bouquet's description (1908) of an apparently

spontaneous attack, with recovery, in a child of fourteen years, following exposure to the sun. More recently Ramsay (1931) describes a case in a child of ten with premonitory symptoms, signs of meningeal irritation, bloody cerebrospinal fluid, and recovery ; and Barber (1936) describes a fatal case in an infant of five months with a spontaneous onset and a picture comparable to that of asphyxia pallida. Post-mortem examination in this case revealed a ruptured dissecting aneurysm of the circle of Willis, and in view of the history of a difficult forceps delivery the etiology of the aneurysm remains in doubt. Barber suggests that while spontaneous subarachnoid haemorrhages in children due to blood dyscrasia, sunstroke, or vasomotor disturbances have a good prognosis, those cases due to aneurysm or congenital deficiency of a vessel-wall are usually fatal : a conclusion which does not accord with what is known of the disease in adults.

Other case reports are those of Dyson (1932)—a spontaneous fatal case in a child of eleven ; and of Murray (1934)—a spontaneous case with recovery and residual symptoms in a boy of the same age.

Case records

The following five cases of subarachnoid haemorrhage, occurring in children apparently otherwise healthy, may therefore be of interest. Three of these cases have been seen by the author in Newcastle during the last few months, and particulars of the other two were obtained from the records of the Royal Victoria Infirmary.

Case 1. Thomas M., aged ten years, while playing football in March, 1935, was seized with sudden intense occipital headache and a paroxysm of copious vomiting. He walked home and on arrival there became unconscious, remaining so for two hours. Eighteen hours later, on admission to the Royal Victoria Infirmary, he was conscious but complained of intense pain in the back of the head and neck. He had neck stiffness and a positive Kernig's sign. The right pupil was larger than the left although both reacted to light ; his optic fundi were normal, his deep reflexes brisk, and the plantar responses flexor ; he had a pulse rate of 120, temperature 99·5° F., B.P. 125/95, and no albumin or sugar in the urine. Four days later the symptoms showed no improvement and lumbar puncture yielded six c.c. of uniformly blood-stained fluid under increased pressure, with some abatement of the severity of the headache. Sixteen days from the onset the temperature still remained between 99·5° and 100·5° F., although the symptoms had almost disappeared, neck stiffness was slight, and Kernig's sign absent. Seven days later the temperature fell to normal, neck rigidity had disappeared, and there were no neurological symptoms or signs. The blood pressure now read 110/85.

Seen in May, 1938, now aged thirteen years, this boy was perfectly well except for a discharging ear of some weeks' standing. He had never had a headache since leaving hospital, and examination was completely negative.

Here is the picture of a sudden, unheralded haemorrhage with a short period of unconsciousness and complete recovery, without residual symptoms, maintained for upwards of three years.

Case 2. Doreen B., aged eleven years, was the third child of a working miner, previously in perfect health and with no personal or family history of headache, migrainous attack, collapse or sudden death. Three weeks before admission to hospital she had complained of severe occipital headache which passed off completely in a few days. Ten days later she ran into the house from an errand, vomited her tea and fell to the ground, conscious, but with

temporary ' loss of use of her legs,' which cleared up in ten minutes. She stayed in bed for three days and on the fourth day visited her doctor, who found nothing apparently wrong. During the next week she was rather listless, but ate well, went to school and did not complain of any headache.

At 2 p.m. on the day of admission, three weeks from the onset of the symptoms, she vomited her dinner, went out to play for an hour, came back into the house and vomited once more. She went to the lavatory and three minutes later was found insensible there, with some twitching of the left arm and rigid legs. She was admitted at 10 p.m. ; since her collapse eight hours previously she had been comatose and had uttered no cry.

On examination the patient was comatose, with limbs slightly flexed and neck extended. She was flushed and the pulse slow (60), full and bounding. The temperature was normal. Running down the midline of the forehead there was a subcutaneous capillary naevus 1½ inches long by ½ inch broad.

Neck stiffness and Kernig's sign were both strongly positive, and elicitation of either caused the patient to open her eyes : the pupils were equal and responded to light, and examination of the optic fundi revealed early bilateral papilloedema. The triceps, knee and ankle-jerks were all brisk, the abdominal reflexes absent, and the plantar reflexes both showed yawning extensor responses.

There were no signs in any other system : the urine contained neither albumin nor sugar, and the blood pressure was 110/70.

On admission eight c.c. of uniformly blood-stained cerebrospinal fluid were obtained by lumbar puncture and the pulse rate immediately rose from 60 to 76 per minute. Left to settle, the fluid twelve hours later showed a dark sediment of red cells with coagulum-free straw-coloured supernatant fluid.

Seventy-two hours later the patient was still comatose but could swallow. The pulse rate had dropped to 66, but rose to 80 on repetition of lumbar puncture. Fifteen c.c. of fluid were removed, similar in appearance to that previously obtained, but showing a brighter yellow supernatant fluid.

For six days after admission the patient's temperature was 100°–100·5° F., and when the temperature fell she had come out of coma, but was apathetic and complaining of severe headache. She was able to feed herself ; neck rigidity was still present, but the plantar reflexes were now equivocal. A Wassermann reaction taken was negative. After another three days the headache disappeared and with it the neck stiffness. There were now no neurological signs, with the exception of resolving choked discs, the plantar reflexes being clearly flexor, and the parents said the child was quieter than usual. During the next month the child gradually returned to complete normality, though the relatives said that her memory seemed impaired. She never at any time complained of further headache and was well two months after the attack (June 16, 1938) when she was discharged.

This history suggests a sudden big haemorrhage, with coma and recovery, following three weeks' premonitory symptoms, with probably at least one haemorrhage of lesser magnitude during that period. The facial haemangioma suggests the possibility of similar intracranial pathology as a source of the bleeding.

Case 3. Thomas N., aged three years, was a fatal case. The history was obtained from the mother's story at the inquest :

' On Tuesday, May 15, 1934, about 2.30 p.m. I heard him crying in the back lane. I went out and saw him holding his head. I asked him what was the matter and he said, " The baa-baa hit me." There were no signs whatever of injury and he soon stopped crying and appeared none the worse. The following day he was playing about and took his food quite well. About 4 a.m. on Thursday, May 17, he woke up crying. I coaxed him to sleep. At 6 a.m. he

awoke crying again and I noticed his neck looked stiff. I thought it was the way he had been lying. He went to sleep again, but when I lifted him out of bed at 8 a.m. he could not stand and his limbs were stiff. He very soon became unconscious, and was sent into the Infirmary that morning.'

On admission the child was unconscious with limbs all rigid and slightly flexed. His head was extended and stiff. He had one generalized clonic convulsion and died within an hour. Lumbar puncture was performed post-mortem, and yielded almost pure blood. Unfortunately there was no autopsy, but in the presence of so definite a history there can be little doubt that this was a rapidly fatal case of spontaneous subarachnoid haemorrhage heralded by thirty-six hours' premonitory symptoms.

Case 4. George H., aged two years, previously perfectly healthy, was admitted to the Newcastle General Hospital on March 23, 1938, with the history of a pyrexial illness of twelve days duration. This began quite suddenly one evening with a bout of screaming, hot flushing, rapid respiration, and above all a marked resentment of being handled or touched in any way. The past and family histories were completely negative.

On examination, the child, flushed and resentful of interference, was lying on his side with his legs slightly flexed. There was some neck stiffness and a positive Kernig's sign, with no evidence of disease in any other system. The temperature was 101·2° F., respirations 28, pulse rate 120, examination of the urine revealed no abnormal constituents.

The next day neck rigidity was much more marked and by lumbar puncture under general anaesthesia, five c.c. of apparently pure blood were withdrawn. This settled into the characteristic two layers of corpuscles and supernatant coagulum-free yellow fluid. Five days later the puncture was repeated with a similar result : and a Wassermann reaction (blood) proved negative.

The child lay for fourteen days completely apathetic, being fed with difficulty ; and at the end of this time return to normality was accompanied by gradual loss of neck stiffness. After twenty-one days the continuous temperature of 100°–102° F., which had lasted in all for practically five weeks, fell to normal, and about the same time the child sat up. A week later the child walked and made a perfect recovery, being discharged quite well eight weeks after admission.

This case of prolonged illness without coma lasting six weeks would appear to suggest a gradual leak of blood into the subarachnoid space over at any rate some days, a syndrome not unfamiliar amongst the cases occurring in adults. Taylor and Whitfield (1936) report eleven of this type amongst their eighty-one cases, and it seems that where the headache is unaccompanied by loss of consciousness the prognosis is uniformly good.

Case 5. Elsie M., aged twelve, was admitted on March 12, 1936. Sixteen hours previously she was playing in the street and suddenly ran into the house holding her head, vomiting, and screaming. Sudden complete blindness followed, and in five minutes she collapsed unconscious into a chair.

At the age of two she was concussed after a fall on the head. She was unconscious for twelve hours and a left internal strabismus followed. She recovered completely in a few days. At the age of seven she had a severe attack of occipital headache with twitching over the right side. For the last six months she had been subject to epileptic fits, Jacksonian in type, starting with twitching of the face, followed by convulsive movements of the right arm and then the right leg. There was never any loss of consciousness. These attacks occurred about once a fortnight and there were usually three or four such fits : they responded to prominal.

On admission the patient was unconscious, the breathing stertorous, and there was general muscular rigidity. It was not recorded whether neck stiffness or Kernig's sign was present. The plantar responses were both extensor :

there was a convergent squint, contracted pupils, and left papilloedema. The pulse rate was 104 and temperature 101° F. Lumbar puncture revealed deeply blood-stained fluid under increased pressure, settling into the characteristic two layers and sterile on culture. A Wassermann reaction on venous blood proved negative. Death occurred forty-eight hours after the onset without recovery of consciousness. There was no autopsy.

The diagnosis here is by no means as clear as in the previous cases, particularly in view of the impossibility of a true evaluation of the history of trauma. Jacksonian attacks, excepting those of a transient nature during the onset of the catastrophe, appear to be rare in association with subarachnoid haemorrhage ; Taylor and Whitfield (1936) report one case preceded by nine months' left-sided attacks. However, in view of the history and the typical nature of the ultimate attack, the most probable diagnosis here seems to be subarachnoid haemorrhage from an intracranial aneurysm, following at least one earlier attack and preceded by local pressure signs.

Commentary

Although neither of the fatal cases came to autopsy, the diagnosis in every instance was confirmed by examination of the cerebrospinal fluid : and the clinical pictures in all five cases are so strikingly similar to those known to occur in adults that it is justifiable, at any rate in cases 1, 3 and 4, where no complicating factors arise, to suspect a similar pathology. Intracranial aneurysm of the type that gives rise to subarachnoid haemorrhage in the healthy young adult has not frequently been recorded in children, but if, as structural evidence suggests, these aneurysms are truly congenital in nature, they must obviously be present (perhaps on occasion only as an initial medial weakness) at birth. The frequently reported association between intracranial aneurysm and coarctation of the aorta is further evidence in favour of a congenital origin, and Fearnsides reports one significant case of a definite aneurysm of the circle of Willis found at autopsy in a child of nineteen months dying of bronchopneumonia complicating gastritis.

In view, therefore, of the clinical findings detailed above, it is suggested that in three of these cases the haemorrhage was in all probability due to rupture of a congenital intracranial aneurysm, and that pathologically as well as clinically these cases are analogous with spontaneous subarachnoid haemorrhage occurring in adults.

Clinically, one or two points of interest arise.

Occupation at onset.—In those children with a definite history of a sudden onset of the illness, the occupation of the child at the probable onset of the haemorrhage was known : three (cases 1, 3, 4) were playing out of doors and one (case 2) ' ran in from an errand.' In this case the later haemorrhage with loss of consciousness occurred while the child was at stool. As demonstrated by Taylor and Whitfield (1936), effort appears to be a factor in provoking haemorrhage into the subarachnoid space.

Pyrexia.—The above authors also found pyrexia, usually between 99° and 101° F., in all their cases which survived sufficiently long ; and in no case without clinical recurrence of the haemorrhage did this pyrexia last longer than seven days. Amongst the five cases in children reported here, one ran a

temperature of 100°–102° F. for five weeks (case 4), this being diagnosed as probably a slow leak ; and in another case (case 1) in which there was no reason to suspect that a recurrence of haemorrhage took place after the first dramatic attack, the temperature persisted at 99·5°–101·5° F. for sixteen days. Such variation in so small a number of cases suggests that in children the heat-regulating mechanism is not so stereotyped in its reaction to the haemorrhage as in adults, a fact which in the absence of lumbar puncture would further complicate the differential diagnosis from some form of meningitis.

Premonitory symptoms.—Of the four cases with a well-defined onset and unconsciousness, three showed some premonitory symptoms—headache (cases 2, 3) and Jacksonian attacks (case 5).

Urine.—Neither glycosuria nor albuminuria was present in any of the three cases in which the urinary findings were recorded.

Prognosis.—From the point of view of prognosis nothing can be added to what has been written of the disease as it occurs in adults, except that residual symptoms were not observed in any of recovered cases (cases 1, 2, 4) during the time since their haemorrhages ; and that, judging from case 1, the ultimate prognosis may not be essentially unfavourable.

Summary

Five cases of spontaneous subarachnoid haemorrhage, two fatal, and all confirmed by lumbar puncture, are described in children between the ages of two and twelve years. They present various clinical pictures strictly comparable to those known to occur in this disease as it affects adults. In one case the presence of a facial haemangioma leads to the suspicion of some similar intracranial pathology as a source of the haemorrhage, and in three of the other four cases the presence of an aneurysm, probably congenital, is suspected. The rôle of effort in the provocation of the attack and the frequency of premonitory symptoms are illustrated, and the pyrexial phenomena associated with the haemorrhage are shown to be somewhat inconstant as compared with the findings in adults.

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CONGENITAL HAEMOLYTIC ANAEMIA WITH NORMAL FRAGILITY OF THE RED BLOOD CELLS

BY

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Case history

The patient is one year and eight months old. The father is healthy ; the mother had a septic infection after the delivery of the second child, which is one month old ; she is still under hospital care. There is no venereal disease or tuberculosis in the family and the Wassermann reaction of both parents is negative. The patient was born at full time with a normal delivery. A few days after birth the parents noticed that the child was extremely pale. They therefore transferred her to a hospital. Blood examination showed a haemoglobin content of only 32 per cent. and 1,900,000 red blood cells per c.mm. The liver and spleen were at that time already enlarged. There had been no disease to account for the anaemia and the white cell count revealed nothing pathological ; a diagnosis was made of congenital anaemia. The child was kept in the hospital for six months and treated with iron, ascorbic acid, ultraviolet radiation and liver preparations. As all these procedures failed to give a therapeutic result, blood transfusions were performed. Altogether, the child received 575 c.cm. of blood in twelve transfusions. The child was discharged from the hospital improved, with a haemoglobin content of 85 per cent. and a red blood count of 4,500,000 per c.mm. The enlargement of the liver and spleen remained unchanged. The child was then sent to an infants' home, where she stayed for four months. After two weeks, it was noticed that the anaemia increased again and a blood count showed a diminution of the red blood cells. For this reason, the parents brought the strikingly pale child to another children's hospital. On admission the child had 41 per cent. haemoglobin and 2,700,000 red blood cells per c.mm. The blood smear, as in former instances, showed only a few normoblasts. The liver was two finger breadths below the costal margin and a firm spleen reached almost to the level of the umbilicus. The child remained in this hospital for four months. She received liver injections without improvement of the anaemia ; only after blood transfusions the child became better. On discharge, the haemoglobin content was 74 per cent., and the red blood cells were three millions. After another four months, on July 7, 1937, the child was admitted under the author's care, again for the reason of her extreme pallor.

On admission, she was fairly well nourished ; she was somewhat small and underweight for her age (8,950 gm.). The skin and mucous membranes were extremely pale. On the lower limbs there were scars of healed impetigo contagiosa. There were no petechiae or other haemorrhages in the skin. The

tonsils were enlarged, but there was no glandular swelling. The liver and spleen were enlarged, being three finger breadths below the costal margin. The spleen was firm. The nervous system was normal ; the static functions were developed according to the child's age.

Blood examination showed 45 per cent. haemoglobin and four million red blood cells. The colour index was 0·5 ; thrombocytes 249,000 ; reticulocytes, 124 per thousand red cells. There was a marked polychromasia, and anisocytosis and microcytosis. The leucocytes was 18,500 per c.mm. ; sedimentation rate, 15 mm. in one hour, 22 mm. in two hours. The bleeding time, coagulation time and the retraction of the blood clot were normal.

The bilirubin of the blood serum was 2·6 mgm. per cent., the serum bilirubin giving only the indirect van den Bergh reaction. Serum protein was 8·12 per cent., non-protein nitrogen 33 mgm. per cent., and blood cholesterol, 120 mgm. per cent. The fragility test of the red blood cells showed haemolysis beginning at 0·47 per cent. sodium chloride solution, which is normal.

Urobilin and urobilinogen were present in the urine, which was otherwise normal. The faeces were of dark-brown colour and normal consistency. The Wassermann reaction was negative. X-ray examination of chest and bones revealed nothing abnormal. The child remained in the ward for two-and-a-half months, feeling well, and taking her food well ; she gained 2,500 gm. in weight during that time

The fragility of the red blood cells was repeatedly checked. As it is evident from table 1, the author, like the other physicians, never found this increased. The bilirubin content of the blood serum, on the other hand, was constantly increased, the level in several investigations ranging from 2·6 to 3·2 mgm. per cent. The blood cholesterol was never increased, repeated examinations showing values between 120 and 160 mgm. per cent. A differential blood count was done almost every second day. A few instances are shown in table 2.

TABLE I

FRAGILITY OF THE RED BLOOD CELLS

	HAEMOLYSIS BEGINNING AT :
November 26, 1936	0·47 per cent. NaCl solution.
February 8, 1937	0·44 „ „ „
July 9, 1937	0·45 „ „ „
July 15, 1937	0·42 „ „ „
July 28, 1937	0·47 „ „ „
August 27, 1937	0·40 „ „ „
September 14, 1937	0·37 „ „ „

Beside the hypochromic anaemia, there was a striking and constant increase of the number of the reticulocytes and comparatively high values of leucocytes. Almost every blood examination revealed occasional erythroblasts. The counting of the eosinophils gave peculiar results ; whereas the number of the eosinophils during the first two weeks of the child's stay in the ward varied between 1 and 3 per cent., reaching only exceptionally 6 per cent., there occurred a sudden rise during the third week. For the last two months the eosinophils ranged between 17 and 21 per cent.

Repeated stool examinations for ova were always negative. There were no signs of allergy, so that there was no obvious reason for the high eosinophil count.

As far as the clinical course is concerned, the fever occurring four times during the two-and-one-half months was the most remarkable phenomenon. Within two days the temperature reached 39° to 40·6° C. ; after two to three

days, it fell spontaneously. These febrile attacks are emphasized as in no instance could any pathological cause be found to explain them. It is noticeable that during the fever period the blood examination did not show essential changes, nor acceleration of the sedimentation rate. The latter varied from 15–16 mm. in one hour and 22–37 mm. in two hours with normal temperature and was 14–33 mm. during the attacks of fever.

TABLE 2

BLOOD COUNTS

	1935 NOV. 26	1936 OCT. 4	1937 JAN. 24	1937 JULY 4	1937 JULY 14	1937 AUG. 14	1937 SEPT. 7
	3 WEEKS OLD	11 MONTHS OLD	14 MONTHS OLD	20 MONTHS OLD	—	—	22 MONTHS OLD
Haemoglobin, per cent.	32	35	41	45	47	50	52
Red blood cells, millions per c.mm.	1·9	2·4	2·1	4	3·4	3·56	3·89
Colour-index	0·84	0·72	0·97	0·56	0·69	0·71	0·68
Reticulocytes	—	590	—	—	124	126	219
Normoblasts	1	4	5	—	1	1	2
White blood cells, per c.mm.	15,800	14,000	14,000	18,500	13,500	19,800	22,100
Lymphocytes, per cent.	58	61	—	55	52	41	49
Monocytes, per cent. ..	—	3	—	—	1	—	—
Juvenile cells, per cent...	1	—	—	1	1	1	—
Rodlike cells, per cent...	15	2	—	2	3	—	—
Polymorphonuclears, per cent.	23	33	—	38	40	40	30
Eosinophils, per cent. ..	3	—	—	3	3	19	21
Basophils, per cent. ..	—	1	—	1	—	—	—
Plasma cells, ...	—	—	—	—	—	—	—
Thrombocytes	—	—	—	146,280	249,000	195,000	248,000

TABLE 3

	JULY 8, 1937 TEMPERATURE 36·6° C.	JULY 15, 1937 TEMPERATURE 38·9° C.
Haemoglobin, per cent.	45	47
Erythrocytes, millions per c.mm.	4	3·4
Leucocytes, per c.mm...	18,500	13,500
Lymphocytes, per cent.	55	52
Juvenile cells, per cent.	1	—
Rodlike cells, per cent.	2	3
Polymorphonuclears, per cent.	38	40
Eosinophils, per cent.	3	3
Basophils, per cent.	1	—
Monocytes, per cent.	—	1
Reticulocytes, per 1,000 white cells	—	124
Thrombocytes	249,000	195,000
Sedimentation time	16/37 mm.	14/33 mm.

Comment

In the first days of life, the infant already showed a severe hypochromic anaemia with swelling of the liver and spleen. In the blood serum the bilirubin

content was increased, the bilirubin giving only the indirect van den Bergh reaction. No bilirubin was found in the urine, which, however, contained abundant urobilin and urobilinogen. The stools were dark brown. The reticulocytes were markedly increased in number. In vital-stained smears a large number of microcytes were found. The fragility test of the erythrocytes against sodium chloride solution was found constantly normal. Finally, there occurred periodically marked sudden rises of the temperature without changes of the white blood cells or increase of the sedimentation rate.

According to these findings, a so-called primary anaemia of the new-born, as described by Ecklin, E. Bonar-Barnet, R. Canina, E. W. Ehrmann, J. A. Foot, F. Gelston, and E. Sappington, McClelland, E. Stransky, and others, can be ruled out. All the results rather speak in favour of an increased haemolysis causing the anaemia, so that the case appears to be one of congenital haemolytic anaemia in an infant. In this connexion the above-mentioned periodical attacks of fever are remarkable. Stress is laid on them because Grob (1934) has described unexplained high temperatures as occasionally the sole symptom of a crisis in haemolytic jaundice. As in this case, Grob found that during these rises of temperature leucocytosis did not occur and the sedimentation time remained unaltered. He also found no shift in the albumin-globulin ratio of the blood plasma. It is, therefore, justifiable to exclude an infectious origin of the fever. Grob claims that it might possibly be a reaction similar to that observed with resorption of haemorrhages.

Haemolytic anaemia in new-born children has been seen repeatedly and described. However, this case is different from all the others on account of the absence of one of the main symptoms of haemolytic anaemia, namely, of the increased fragility of the erythrocytes. I have had the opportunity of observing in my ward of the Children's Hospital of the Berlin University two similar cases in infants. In these infants also I found all the symptoms of haemolytic anaemia except for the increased fragility. I have not been able to trace similar observations in the paediatric literature ; whereas, A. Adler (1927) has described three adolescents of fifteen, sixteen and nineteen years respectively and a forty-years-old woman, all of whom showed anaemia with enlarged spleen, bilirubinaemia, with an indirect van den Bergh reaction, urobilinuria as well as a marked increase of the reticulocytes. Thus all the symptoms of haemolytic anaemia were present, while the fragility test of the erythrocytes against salt solutions was constantly normal. Hereditary influence could not be proved in any of these cases nor was it possible in the present case. At any rate, physical and blood examination of the parents did not reveal any essential point in favour of an existing haemolytic anaemia.

O. Naegeli already pointed out that even in typical cases of haemolytic jaundice in adults the diminishing of osmotic resistency (increased fragility of the erythrocytes) may, rarely, be lacking temporarily. In one of his cases, for instance, the abnormal fragility of the erythrocytes had only become manifest during a stay in the high mountains. It was also noticed in these rare cases that increased fragility of the erythrocytes may be elicited by means of certain artificial influences as, for instance, irradiation of the spleen with

ultra-violet rays. This method was tried in the case reported here, without success.

Though the increased fragility of the erythrocytes is lacking, all the other symptoms in the present case tell in favour of a congenital haemolytic anaemia. The observation points to the fact that no matter how much value is attached to the fragility test, a decisive significance in making the diagnosis cannot be attributed to it. In this connexion, an observation made by E. Lesné, R. Launey and I. Hurez (1935) is noticeable. These authors report the case of a woman suffering from typical haemolytic jaundice ; her spleen was greatly enlarged and the fragility of the erythrocytes markedly increased. One of her eight-year-old twins also had a much enlarged spleen. The fragility of the erythrocytes, however, was almost normal. The twin sister's spleen was only slightly enlarged ; the child was anaemic while the fragility test was normal. Unquestionably from this observation, it must be concluded, as the authors emphasize, that in haemolytic anaemia the symptoms of the disease may not all be present at the same time. This has long been known as regards the jaundice. Because this symptom is so often lacking, it is customary to-day not to use the term ' haemolytic jaundice,' as formerly, but plainly haemolytic anaemia (with or without jaundice). By the way of parenthesis, it may be mentioned that G. Frontali (1936) described typical haemolytic anaemias in children in whom the osmotic resistance of the erythrocytes was found to be even constantly increased.

Summary and conclusion

The history of a one-year-and-eight-months' old girl is reported in whom, in the first days of its life, a severe hypochromic anaemia together with enlargement of the liver and spleen was already present. Further examination showed all the typical symptoms of a congenital haemolytic anaemia ; the fragility test of the erythrocytes, however, was normal throughout the observation period. During periodically occurring rises in temperature, no essential changes in the blood could be demonstrated, nor an acceleration of the sedimentation rate. These febrile attacks are considered as equivalents of haemolytic crises. The disease could not be proved to be inherited.

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CASE REPORTS

HYDATID CYST OF THE SPINAL CANAL SUCCESSFULLY TREATED BY OPERATION

BY

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This case of solitary hydatid cyst of the spinal canal is reported not only for its rarity but also because it shows that the results of operative treatment of this condition, of which the records in this country are comparatively few, may be dramatically successful.

Clinical record

A girl, aged nine years, the daughter of poor parents, began to complain in October, 1933, of pains in the thighs and, later, in the lower part of the spine. Early in 1934 she attended the surgical out-patient department and in February was admitted to a medical ward for observation. Radiological examination of the spine and of the hip-joints revealed no abnormality ; the electrical reactions were normal except for a slight weakness of some of the muscles of the right leg. As nothing was found to account for her symptoms, she was discharged after eight days with the diagnosis of subacute rheumatism and resumed her attendance at the surgical department. During the next ten weeks her condition steadily became worse, and on May 1, 1934, she was examined by one of us (J.S.Y.R.). The following is a brief account of the history and clinical signs then elicited :

In the family history there was nothing noteworthy and the patient herself had always been strong and healthy until the onset of her present illness. The pains, of which she had now been complaining for about seven months, occurred first of all in the left thigh and knee and later in the right thigh ; they were not severe to begin with, but had gradually become worse. Early in 1934 bouts of pain, localized in character and always in the same spot, developed in the lower part of the back. This pain was not present when she was walking, but came on when she was sitting in a chair or lying in bed, and was then so sharp and agonizing that it kept her awake and crying most of the night. She had also some pain in the left hip, which made her walk with a limp. In the early part

of the year, in her father's words, ' She could run a hundred yards like a hare and then collapse ' ; now she could walk only a short distance, and when going upstairs had to haul herself up by the hand-rail.

Examination did not reveal any spinal deformity or any sign of rigidity. Bending the body backwards did not cause pain, and if pain were already present did not increase it. The site of the pain was in the region of the three upper lumbar vertebrae ; but pressure over that area did not evoke it, although there was a slight hyperaesthesia of the skin. She had a peculiar waddling walk, with a limp on the left side. Passive movements showed no limitation of movements at hips or knees, but there was some pain on movement at the left hip-joint. The muscles of both legs were soft, flaccid and somewhat atrophied. The power to resist movements of the legs and the freedom and rapidity of active movement were all diminished. The knee-jerks were absent and there was anaesthesia of the legs. There was no disturbance of function of bladder or bowel. An examination of the blood showed haemoglobin 83 per cent., red cells 5,000,000 and white cells 7,300 per c.mm. No abnormal cells were found and no increase in eosinophils.

On May 7, an x-ray examination was again made, and the radiologist reported that he failed to find evidence of bone disease either in the hips or in the lumbar spine.

From the persistent recurrence of localized pain in the upper lumbar spine, the pain in the thighs, pointing to a referred pain from pressure in the same region of the spine, and the flaccid paresis of the legs such as occurs in a compression myelitis, the tentative diagnosis was made of intraspinal tumour and the case was referred for a surgical opinion to the late Professor John Anderson. Considering her peculiar walk and limp and the pain on movement at the left hip, Professor Anderson inclined to the view that there might be an early tuberculosis of the hip-joint, even although x-ray examination had shown nothing abnormal, and arranged to admit her to his ward when a bed was available. By June 7, however, her condition was changing so rapidly for the worse that she was admitted as an urgent case. On the following day cisternal puncture was performed under light anaesthesia and lipiodol injected ; the skiagraph showed spinal blockage at the level of the first lumbar vertebra (fig. 1).

On June 28, under rectal ether, Professor Anderson exposed the spines from the twelfth dorsal to the fourth lumbar, and performed laminectomy of the first, second and third lumbar vertebrae. A greyish-white cystic mass was found lying extradurally in the canal and was easily shelled out. The cyst extended from the lower border of the first lumbar to the upper border of the third lumbar vertebra, measuring about 2 inches in length by $\frac{3}{4}$ inch in greatest breadth. The results of the operation were excellent. By August 4 the patient was up and walking with support ; by August 21 the limp had gone, and although still unsteady she was walking much better ; by August 30 sensation was normal, and, except for a little difficulty in balancing, she was walking very well. She was discharged from hospital on September 12, 1934, completely cured. An x-ray examination made later showed that the lipiodol now passed well down to the lower end of the canal (fig. 2). When last seen in April, 1938, she looked strong and fit and showed no abnormality in her walk.

Pathological examination

The specimen consisted of the two halves of an ovoid unilocular cyst measuring approximately $1\frac{1}{2}$ inches in length by $\frac{3}{4}$ inch in greatest breadth. The wall of the cyst was composed of a whitish, gelatinous, translucent tissue resembling coagulated egg-white, and was apparently homogeneous throughout.

Both the external and internal surfaces were perfectly smooth and there were no ingrowths. On the inner surface one minute pinkish spot was just visible to the naked eye, and on microscopic examination of a scraping from the wall at this spot, several typical hydatid hooklets were found amongst amorphous debris (fig. 3). From the characters of the cyst wall and the size of the hooklets it was clear that the mass from the spinal canal was the cystic stage of taenia echinococcus. A section from the cyst wall showed the laminated cuticula and lining proliferative layer of a hydatid ; no scolices were found. The cyst

FIG 1.—X-ray five hours after injection of lipiodol, showing spinal blockage at the level of the first lumbar vertebra.

having ruptured, no fluid was available for examination. The source of the infection was not discovered ; the patient was not known to have been in contact with dogs.

Commentary

The spinal canal is one of the more unusual sites of hydatid cyst.

Neisser, in his collection of 986 cases of echinococcus disease in the literature, found only thirteen cases with cysts in the spinal canal (quoted by Leuckart, 1886). Lyon (1902) in an exhaustive review of echinococcosis in North America

Fig. 2.—X-ray showing lipiodol passing freely down to lower end of spinal canal.

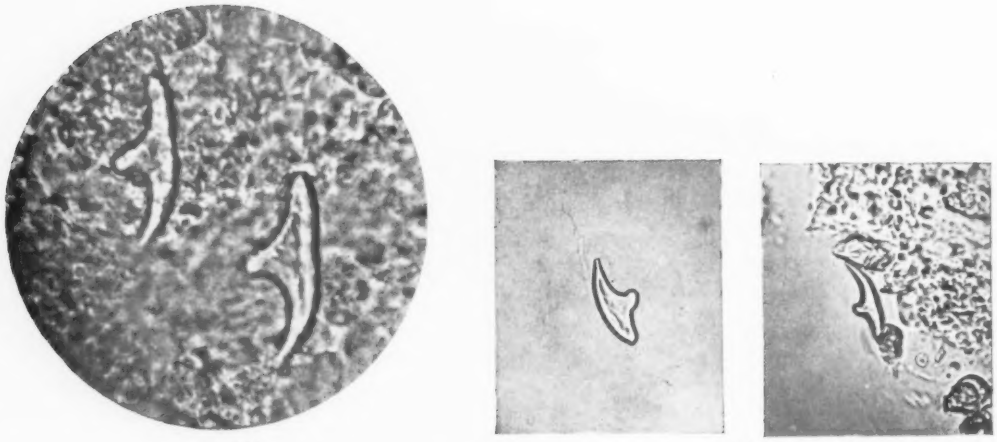

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FIG. 3.—Hooklets from hydatid cyst of spinal canal.

did not record a single instance of intraspinal cyst in the 241 cases of hydatid disease which he collected from the literature up to 1901.

In this country, where hydatid disease is uncommon, a cyst in the spinal canal is, at the present time, an extremely rare occurrence ; nevertheless records of a considerable number of cases are to be found in the English literature, especially in the latter part of the past century and in the early years of the present. In most cases the diagnosis was made post mortem and the records of successful operative treatment are few.

Ogle (1860) refers to a case of hydatid cysts within the spinous process of the seventh cervical vertebra and causing compression of the cord. Fagge (1871) mentions a case observed at post mortem, and Murchison (1885) a specimen in the Middlesex Hospital from a case of paraplegia caused by compression of the cord by secondary hydatids. Ransome and Anderson (1891) record a case in which laminectomy, performed for a supposed spinal tumour, failed to reveal the intraspinous hydatid cyst found later at autopsy. Colman (1899) quotes Gowers for a case of spinal hydatid in which ' Mr. Horsley trephined the spine and a quantity of cysts the size of peas were found compressing the cord.' Colman collected from the literature thirty-six records of spinal hydatids and added a case observed by himself of paraplegia produced by an extradural cyst in the spinal canal of a boy aged ten years ; the diagnosis was made post mortem. In a case recorded by Barrs and Trevelyan (1899) multiple hydatids were found in the spinal canal ; they had produced symptoms of acute myelitis. Tytler and Williamson (1903), in reporting successful operative treatment by laminectomy in a case of spinal hydatid cysts with severe compression myelitis, pointed out that a study of the recorded cases showed that spinal hydatids were usually external to the dura, and being mostly on the posterior aspect were usually favourably situated for operative removal. In a survey of hydatid disease in children including cases published since Lyon's paper of 1902 Mills (1926) found few in the spinal canal ; in addition to Colman's case, he mentions one reported by Fournier (1918) in a boy aged twelve, with successful operation ; the cyst had produced a paraplegia. He also quotes a record by Owen of Melbourne (1905) of five cases of spinal hydatids treated by operation. Another case of successful operation is reported by Gill and Bullock (1919). These authors comment on the small number of records of successful operations for hydatids in the spinal column, and consider that by the time a diagnosis can be made the disease is usually too extensive for operation. The preoperative diagnosis of hydatid of the spine can never, in their view, be more than a probability. Bériel and Leriche (1923) record a hydatid cyst of the sacrum which compressed the sacral nerves and caused sciatica ; in this case the preoperative diagnosis of hydatid disease was made tentatively. Recently in this country Lambert Rogers (1938) has removed from the spinal canal an extradural hydatid which had produced a compression paraplegia.

No attempt has been made to give a complete review of the literature on this subject and attention has been confined to illustrative cases, mainly from this country. In the literature of countries where, as in parts of South America and Australia, there is abundant clinical material for the study of echinococcosis, numerous examples of spinal hydatid, some with successful operative treatment, are to be found. But most of these records are in journals not available in this country, and it has not been possible to verify the references.

The present case emphasizes certain points which emerge from the records. It brings out the great difficulty which the diagnosis of hydatid disease of the

spinal canal always presents ; the intradermal reaction of Casoni and the complement-fixation test would doubtless have been of the greatest value, but in the present case, in a locality where hydatid disease even in its commoner sites is seldom met with, there was nothing in the history or in the preoperative clinical findings to suggest that echinococcosis should be considered in the differential diagnosis. On the other hand the case serves as a reminder that the site of election of hydatid cysts in the spinal canal, extradurally and on the posterior surface of the cord, facilitates operative removal, and that the results of operation are frequently most favourable.

Summary

A case is reported of hydatid cyst in the spinal canal of a child ; pressure on the cord had produced paresis and parasthesia of the lower limbs ; operative treatment by laminectomy resulted in a complete cure.

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TETANY IN THE NEW-BORN

BY

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Although the diagnosis of spasmophilia, or tetany, is often made in new-born infants manifesting muscular twitching or convulsions, it is rarely upheld by estimation of the level of serum calcium. The following case of 'clinical' tetany was instructive in that the child was delivered by Caesarean section before labour had started, thus eliminating possible sources of intra-cranial injury produced during labour, and facilities were present for accurate biochemical analysis of the serum and for the examination of the electrical reactions of the muscles.

Case Record

1ST DAY : The infant, a male, was delivered by Caesarean section. There was no delay in the establishment of respiration. Birth weight 8 lb. 13 oz.

2ND TO 9TH DAY : The child appeared perfectly normal and sucked strongly. Breast feeding was only poorly established, and the feeds were therefore supplemented with a dried milk.

10TH TO 12TH DAY : The baby had several attacks of twitching, a typical attack being as follows : Both hands went into Trousseau's classical position, the metacarpo-phalangeal joints being flexed, fingers extended ; then the wrist flexed ; finally the elbow was flexed in a series of jerky movements. The toes twitched rhythmically, and the lower limbs were flexed in a similar manner. Simultaneously the eye-lids flickered rapidly ; the lower jaw jerked up and down ; and the head jerked in a rotatory manner to the right. During an attack there was no raised intra-cranial tension as judged by the tension of the anterior fontanelle. In the intervals between the attacks, the child took its feeds normally and appeared contented. Clinical examination revealed no abnormality in the respiratory, cardio-vascular, or central nervous systems. No abnormal constituents were found in the urine by the routine laboratory methods. Attacks could be induced by pressure or pinching of upper and lower limbs. A provisional diagnosis of hypo-calcaemia was made, and the following treatment instituted :

1 c.c. calcium gluconate, intra-muscularly twice a day.
Chloral hydrate, 1 grain three times a day by mouth.

14TH TO 16TH DAY : The treatment produced no satisfactory results ; indeed, the attacks became more frequent and severe. The initial phase was as

described above, but in several attacks respiratory spasm gradually appeared, leading to cyanosis. As many as nineteen attacks were recorded in twenty-four hours.

17TH DAY : Blood was obtained by heel puncture and serum calcium estimation estimated. This was done in duplicate and controlled. It showed the serum calcium to be 5·8 mgm. per 100 c.c.

The electrical reactions of the muscles were investigated and found to be as follows :

1. Anodal opening contraction and kathodal opening contraction were greater than both closing contractions.

$$\text{A.O.C.} > \text{K.C.C.}$$

2. When the current was allowed to flow for one or two seconds, the limb under examination went into the typical Trousseau position, but the contraction was limited to the muscle stimulated.

These findings were consistent with a diagnosis of spasmophilia and contrary to upper motor neurone convulsions.

The following treatment was then carried out :

Calcium lactate, 5 grains six times a day by mouth.
Solution of irradiated ergosterol, 4 minims three times a day by mouth.
Chloral, 1 grain four-hourly by mouth.
Intramuscularly, calcium gluconate 5 c.c.

17TH TO 21ST DAY : The fits diminished in number and severity during the next forty-eight hours.

Serum calcium : 7·0 mgm. per 100 c.c.
Serum phosphorus : 5·2 mgm. per 100 c.c.

When no spasms had been noted for forty-eight hours (four days after beginning treatment), the treatment was modified as follows : Intra-muscular injections were discontinued ; the chloral was reduced to eight-hourly doses of 1 grain, and finally discontinued.

24TH DAY : The child's condition remained satisfactory for a further three days, when two mild attacks were observed. The following addition to treatment was then made : parathormone, 4 units subcutaneously daily for two days.

30TH DAY : The dose was then reduced by one unit each day, and finally discontinued. No further attacks were noted, and the child was perfectly well on discharge from hospital.

36TH DAY : The following investigations were carried out prior to discharge : Serum calcium : 10·5 mgm. per 100 c.c. Electrical reactions were normal. No typical spasm was noted when the current was allowed to flow for several seconds.

All treatment was discontinued on discharge with the exception of 1 teaspoonful of cod liver oil emulsion once a day. At the age of three months the child was normal and thriving satisfactorily.

Thanks are due to Dr. A. McCance for the biochemical investigations, Dr. Cooksey for investigating the electrical reactions, Dr. Wilfrid Sheldon for much help and guidance in the treatment of this infant and Mr. J. H. Peel for permission to publish the case.

CRANIO-CARPO-TARSAL DYSTROPHY

An Undescribed Congenital Malformation

BY

E. A. FREEMAN, F.R.C.S., Hon. Orthopaedic Surgeon, and

J. H. SHELDON, M.D., F.R.C.P., Hon. Physician to the Royal Hospital, Wolverhampton

The two children who form the subject of this paper were shown at the Section for the Study of Disease in Children of the Royal Society of Medicine on March 25, 1938, when it was considered that they were examples of a previously undescribed condition (Freeman and Sheldon, 1938). Both cases exemplify a number of similar features, and as there can be little doubt that these go together to form one disease entity, a full account is offered in view of the fact that this appears to be its first description.

Clinical Records

Case 1. A male aged two years nine months, with no relevant family history or consanguinity of parents, was an elder child, the second baby being normal. The patient was a seven-and-one-half-months baby, born by normal labour without instruments. The weight at birth was 3½ lb. including clothes. His appearance at birth caused such consternation ' that he was taken downstairs and shown to the grandmother, and then put out to die.' The legs were born fully flexed on the trunk in a ' Buddha ' position, and at the back of the head was a lump described as ' jelly-blood ' which disappeared naturally in some three or four days. The nature of this is uncertain. Its description is not that of a cephalhaematoma, and neither by x-rays nor clinically is there now any evidence of abnormality in the posterior part of the head. The face was abnormal. The lower forehead and eyebrows were occupied by a soft but prominent transverse swelling and the eyes were buried so deeply that they were hardly visible. The nose could barely be recognized and the mouth was small. In addition to these features, the hands showed ulnar deviation and the feet a severe degree of talipes equino-varus. In spite of the immediate reaction to his appearance in the world, efforts were made to rear him, which were all the more difficult in that for some days he was unable to suckle owing to difficulty in swallowing. He was fed with drops of fluid from an eye-dropper, since more than one drop at a time ' stuck in his throat.' Eventually swallowing became normal, and he was reared on a dried milk. On account of the deformity in the feet he was sent to the Orthopaedic Department of the Royal Hospital, Wolverhampton, when a fortnight old. He continued to receive treatment for the feet until May, 1937 (age twenty-three months), when he was admitted under Mr. R. Milnes Walker, F.R.C.S., Hon. Surgeon to the

Royal Hospital, Wolverhampton, on account of a swelling in the right loin. At operation this was found to be due to torsion of an imperfectly descended testicle, the organ being removed as it was partly gangrenous. He made a

FIG. 1.

good recovery from the operation, but before leaving hospital he developed a pneumonia followed by empyema, surgical drainage of which led to a complete recovery. Since then he has been receiving further orthopaedic treatment, and his general health has remained good.

Present Condition.—Length : 2 feet 8 inches. Weight : 27½ lb. Routine clinical examination reveals no abnormalities beyond those detailed below. Mentality is fair. He is able to talk, to frame short sentences and can repeat simple nursery rhymes. He has an unusually good ' musical ' ear. During the first eighteen months of life the mentality was backward, but he has been catching up since, so that he is now not far behind the normal for his age.

FACE.—This is the most obvious feature and is shown in fig. 1. Across the lower forehead just above the eyebrows is a soft, subcutaneous swelling, which is shiny in reflected light and moves with the facial muscles. Similar

FIG. 2.—X-ray of skull of case 1. (The lower jaw is obscured by the nurse's hand.)

subcutaneous ' bosses ' are present on each side of the upper forehead and are clearly visible in the photograph. The eyes are deeply sunken, and there is an internal strabismus of the left eye. The eyes appear to be more widely separated than normal. The bridge of the nose is broad and disproportionately big in comparison with its lower part, which is small and narrow and does not rise above the face to a normal extent. This feature was more marked at birth. The nasal openings are small. Both cheeks are abnormally fat, rosy and shiny. (This is well seen in the photograph.) The distance from the nose to the upper lip is abnormally great, and at the first view of the child this is probably the most striking feature. The mouth is small in proportion to the

rest of the face, and the upper lip appears smaller than the lower. The tongue is small. That the mouth really is small is seen from the fact that at the age of two years it was almost impossible to introduce a wooden spatula, and a

FIG. 3.

tea-spoon could not be admitted. The palate is highly arched, but the teeth are normal except for caries. There is an unusually well-marked dimple on the mid-point of the chin. Taken all in all, the part of the face below the eyes appears too small in proportion to the forehead.

An x-ray photograph of the skull is shown in fig. 2. On comparison with the normal skull there are three abnormalities : (1) The floor of the skull in the anterior fossa slopes steeply upwards towards the frontal bone. (2) There appears to be a partial failure of union between the frontal bone and the floor of the skull, so that there is a free prolongation downwards of the lower end of the frontal bone. (3) In relation to the total antero-posterior length of the skull, the part occupied by the nasal and facial bones appears to be less than normal. Antero-posterior x-ray examination of the skull did not reveal any abnormal features.

HANDS.—The hands show ulnar deviation, but no associated bony

FIG. 4.—X-ray of skull of case 2.

abnormality can be seen on x-ray examination. Without treatment there has been considerable improvement in the function of the hands since birth. The hands are covered with a firm fat, like that on the face. On the flexor surfaces of the first phalanges of both hands there is a considerable degree of horny thickening of the skin and subcutaneous tissues.

FEET.—The feet show an extremely severe bilateral talipes equino-varus, with no unusual features. They have received a good deal of treatment with disappointing results. Correction was first attempted by means of pads and strapping by Brockman's method. Little progress was made, and plaster correction was resorted to, again without success. More recently an attempt

has been made to free the scaphoid from its attachments on the inner side, but further bony correction will probably be necessary at a later date.

Case 2. A female, age nineteen months, was an only child, with no relevant family history and no consanguinity of parents. She was an eight months' child, born by normal labour. The weight at birth was 4½ lb. It was immediately obvious that the hands and feet were deformed, but nothing unusual was noticed in the face except that the mouth was small. She was able to suckle and there was no difficulty in swallowing. She was breast-fed for fourteen days, and then given a dried milk. As with the previous case, she was brought at an early age to the Orthopaedic Department of the Royal Hospital on account of the feet.

Present Condition.—Length : 2 feet 7 inches. Weight : 32 lb. Routine clinical examination revealed no abnormalities beyond those detailed below. Mentality is fair—she can say simple words, but not sentences.

FACE.—The appearance in general is similar to that of case 1, but is much less marked. It is shown in fig. 3, which, however, makes the face appear more normal than it actually does to the eye. At the Royal Society of Medicine several observers took the children for brother and sister. There is no supra-orbital swelling and no subcutaneous bosses over the forehead. The eyes are more deeply sunken than normal, though not to the same extent as in case 1. The upper part of the nose is broad in proportion to the lower half, which does not rise out of the face to a normal extent. The space between the lower end of the nose and the mouth is big, and the mouth is smaller than normal though it is not suggested by the photograph. There is no dimple over the symphysis of the chin. X-ray examination of the skull (fig. 4) shows the same general appearance as in case 1. There is the same defective union between the frontal bone and the floor of the skull, with a prolongation downwards of the lower end of the frontal bone. The floor of the skull does not rise up so sharply as in case 1, nor do the facial and nasal bones appear so shallow.

HANDS.—These show ulnar deviation as in case 1, and there is no bony abnormality to be seen by x-ray examination. On the flexor surface of the first phalanges there is the same horny thickening as in case 1.

FEET.—These show a severe bilateral talipes equino-varus with extreme adduction and inversion. As with the previous case, much treatment has been necessary. Correction was first attempted by Brockman's method of padding and strapping, and later plaster correction was used, also without success. Operation was then performed, the scaphoid being freed along its inner attachments and the feet put in plaster again, but there is still marked deformity.

Discussion

These two children each show a collection of identical features, the only differences being in their sex and in the fact that the facial appearance is much more normal in the second case. These features are :

(1) They are both first children.
(2) Premature birth (7½ and 8 months), to which the small weight is attributable.
(3) An abnormal facies.
(4) An abnormal x-ray appearance of the anterior end of the skull.
(5) Ulnar deviation of the hands with thickening of the skin and subcutaneous tissues over the flexor surface of the first phalanx of the fingers.
(6) Severe talipes equino-varus.

The simultaneous appearance of these various features in two children leaves little room for doubt that they hang together as a single disease entity, the most probable explanation of which is that it is due in each case to a similar genetic abnormality. Although they both come from the same town, they do not appear to be related, although it has not been possible to take the enquiries very far back. The grandparents were not related, and of their sixteen great-grandparents only twelve can be identified, but these were not related. Inasmuch as the condition appears to be an undescribed one, the name of ' cranio-carpo-tarsal dystrophy ' has been provisionally applied to it.

Thanks are due to Dr. G. E. Dyas, Hon. Radiologist to the Royal Hospital, Wolverhampton, for his help with the x-ray examinations.

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BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE ELEVENTH ANNUAL GENERAL MEETING

The Eleventh Annual General Meeting was held at the Grand Hotel, St. Andrews, on Friday and Saturday, May 20 and 21, 1938.

First Session (May 20, 10.15 a.m.)

Business Proceedings : The President, Dr. J. Wilkie Scott (Nottingham), was in the Chair, and there were present 49 members and 11 guests.

The Minutes of the last Meeting were read and approved.

The following Officers, and Honorary, Corresponding and Ordinary Members were elected :

President : 1938–39, Dr. H. C. Cameron (London).

Secretary : Dr. A. G. Maitland-Jones (re-elected).

Treasurer : Dr. Donald Paterson (re-elected).

Representative for Scotland : Dr. S. G. Graham (Glasgow), in place of Dr. William Brown.

Honorary Member : Dr. Leonard Findlay (Past President).

Corresponding Member : Professor Dr. E. Gorter (Holland).

Ordinary Members : Dr. A. W. Franklin (London), Dr. J. H. Hutchison (Glasgow), Dr. D. N. Nicholson (Edinburgh) and Dr. C. T. Potter (London).

The Treasurer's Report was received and adopted.

The President then proposed from the Chair that, ' The Members of the British Paediatric Association offer sincere congratulations to Dr. Robert Hutchison upon his election as President of the Royal College of Physicians. They also desire to express their gratification that he has received this distinction, and their hope that his tenure of office will be a long and successful one.' This resolution was passed with acclamation.

After some discussion the Meeting then decided :

(1) That a letter be sent to the Canadian Society for the Study of Diseases of Children inviting members of that Society to join in the Annual Meeting of 1939 ;

(2) That candidates engaged in the administrative side of Paediatrics or acting as Medical Officers to schools are eligible for membership of the British Paediatric Association.

(3) That the Executive Committee decide on a subject for discussion at the Annual Meeting in 1939 and invite members of the Association to take part in such discussion.

The place of meeting for next year was then discussed.

Scientific Proceedings :

1. Professor Charles McNeil (Edinburgh) : ' Pleuro-pneumonia and empyema (pneumococcal).' The term ' meta-pneumonic empyema ' suggested a complication occurring after the acute phase of pneumonia, but in such cases the morbid process which ended in empyema had begun during the phase of pneumonia as an acute pleurisy. The first stage of acute pleurisy was a sero-fibrinous effusion and might not go beyond this ; the further stage of empyema was determined by an infiltration of pus cells into the fibrinous exudate and the passage of these pus cells into the serous effusion. It was suggested that cases of pneumococcal empyema showed on the clinical side a counterpart of these pathological stages : a first stage

of acute thoracic or abdominal pain, with unusual embarrassment of breathing and general distress and early physical signs of consolidation ; a second stage, corresponding to the separation of the pleural surfaces by effusion, when there was relief of pain and easier breathing ; and a third stage, generally meta-pneumonic, in which the serous effusion became purulent and in which the clinical counterpart consisted of persisting signs of consolidation and a slow decline in the general condition.

2. Dr. H. C. Cameron (London) : ' Spontaneous resolution in haematogenous staphylococcal osteomyelitis.' Staphylococcal osteomyelitis was certainly becoming rarer, probably also it was becoming less severe. Often the more striking symptoms of bacteraemia were absent. Rigor, sweats, delirium and the metastasis might appear only after a long delay. As in the comparable case of a perirenal infection, spontaneous resolution was by no means uncommon. The metastasis often involved a small and superficial branch of the periosteal or medullary anastamosis. Immediate drastic surgical intervention, before the outlines of the infected area had become established, destroyed more bone than was ultimately to suffer irreparable damage, removed together with the infected focus all the barriers which were being formed to localize and protect, and was apt to be followed by an exacerbation of the bacteraemia. Many surgeons now advised conservative treatment. The history was selected of three patients with osteomyelitis simultaneously under observation, all of whom had made a spontaneous recovery without operation. The first in the neck of the femur with arthritis of the hip-joint, the second in the neural arches of the lumbar vertebra with staphylococci in blood and cerebro-spinal fluid, and the third with severe staphylococcal fever without anything but the most transient pain and minimal swelling over the lower end of the femur.

3. Dr. J. S. Y. Rogers (Dundee) and Dr. G. R. Tudhope (introduced by Dr. Rogers) : ' A case of hydatid cyst of the spinal canal with successful operation ' (see p. 269).

4. Dr. James H. Hutchison (Glasgow) (introduced by Dr. Stanley Graham): ' The role of copper in iron-deficiency anaemia.' Nine cases of nutritional anaemia have been studied. In six cases large doses of ferrous sulphate were given orally for varying periods. This was then discontinued, and when the haemoglobin levels again became constant minute doses of copper sulphate were given and the effect on the haemoglobin recorded. In the other three cases small doses of ferrous sulphate were given for several weeks in an attempt to produce an iron-storage in the body without changing the haemoglobin level. The iron medication was stopped and after a variable time copper sulphate was given, and any mobilization of the stored iron for haemoglobin formation calculated. In each case the amount of iron stored in the body and the percentage of retained iron utilized for the formation of haemoglobin were demonstrated by an iron-balance study. The results of these researches on one typical case from each series were demonstrated, and showed that copper in the presence of adequate iron storage in the liver is capable of stimulating haemoglobin synthesis. Regarding the mode of action of copper it was suggested that a sufficient concentration of iron in the blood serum to meet the needs of the bone marrow was ensured by the catalytic action of copper, which liberated iron from the liver into the systemic circulation.

5. Dr. T. Colver (London) (introduced by Dr. Paterson) : ' Icterus gravis neonatorum.' The frequent reports of cerebral sequelae of icterus gravis neonatorum prompted a review and follow-up of the clinical material at the Hospital for Sick Children, Great Ormond Street. In the series there were included all those cases of haemolytic anaemia which were complicated by jaundice within the first 48 hours of life, and in which there had been excluded (1) infection, (2) syphilis, (3) congenital obliteration of the bile ducts, and (4) acholuric jaundice. The presence of erythroblastaemia, itself a secondary sign, was not insisted upon. In the series nine cases were jaundiced at birth. This was the worst prognostic group, there being only one survivor. Haemoglobin levels below 60 per cent. (Haldane) were present in 90 per cent. of the cases in which an adequate series of blood examinations had been made. Erythroblastaemia was present in 85 per cent. In seven cases (14 per cent.) there was a family history of ' icterus gravis.' Death occurred in 62 per cent. of cases. Figures could not actually be brought forward to support the therapeutic value of either blood transfusions or intramuscular blood injections. Quite sufficient to account for this was the fact that so many cases were admitted late in the course of the disease. It was clear, however, that many cases survived in the absence of treatment. The single survivor of the nine cases in which jaundice was present at birth received no treatment. This was a severe case and there has been complete recovery. The follow-up was successful in nine cases which survived the early stages. Of this group one is mentally deficient, one has a mild hemiplegia and six are healthy both mentally and physically. The ninth case died at the age of fourteen months from intercurrent infection.

6. Dr. L. H. F. Thatcher (Edinburgh) : ' Acute leptomeningitis ; listerella monocytogenes

infection.' This little known organism may be the cause of acute suppurative meningitis, especially in babies ; only eight cases have been reported, the first in 1933 ; seven of them were in America and one in Scotland (1935). With one exception, they died within a few days ; she was alive ten weeks after the onset of illness, showing serious physical and mental changes. This ninth case, a boy aged seventeen months, died after an illness of a week's duration ; clinically, it was a purulent meningitis ; but surprisingly only about thirty cells in the high-power field (fresh uncentrifuged specimen) were found, polymorphs and lymphocytes being present in approximately equal numbers. A ' diphtheroid ' organism was seen, but full investigation proved this to be listerella monocytogenes ; there were no suspicious contacts. The infection is of special interest because animals are likely to be the source of it. In 1926 there was a severe epidemic among the rabbits and guinea-pigs of the Cambridge Field Laboratories ; the features were a monocytosis of the circulating blood and tiny areas of necrosis in the liver ; a new bacillus was isolated. A little later, the same disease was recognized in small rodents in South Africa, and the name given to the causative organism after consultation between the workers in these widely separated fields. Other species may be infected : the organism has been found in sporadic encephalitis of cattle (America) ; in sheep with encephalitis (Australia, New Zealand and America) ; moreover, cases have occurred among laboratory chickens at Princeton University.

7. Dr. R. E. Smith (Rugby) (introduced by Dr. A. G. Maitland Jones) : ' The late descent of the testicle.' (This will appear in full in a future number of the *Archives*.)

8. Dr. C. Paget Lapage (Manchester) : ' A note on the treatment of thread worms.' The possibility of the parasites being cleared away by a bismuth or barium meal supplemented if necessary by a barium enema to fill the colon was discussed. This method had been tried in some fifty cases with good results in a large proportion of them. Bismuth is probably more effective than barium, though it is more expensive. The French writers have used bismuth in moderate doses for some time, but from a therapeutic rather than from a mechanical point of view. This mechanical action is the main basis of the idea of the bismuth meal, though bismuth appears also to have some toxic action on the thread worm.

Second Session (May 21, 10.30 a.m.)

9. Dr. A. V. Neale (Birmingham) : ' A case of pineal tumour ' (see page 241).

10. Dr. J. H. Ebbs (Birmingham) (introduced by Prof. L. G. Parsons) : ' Oesophagitis in infancy ' (see p. 211).

11. Dr. A. G. V. Aldridge (Birmingham) (introduced by Dr. J. M. Smellie) : ' Blood transfusion in dehydration in infants.' At the Birmingham Children's Hospital a study has been made of the effect of blood transfusion in cases of dehydration, and it was found that blood transfusions not only did not cause improvement in such cases but actually often caused a deterioration of the patient's general condition. In cases of dehydration there is a varying degree of concentration of the blood, with increase in the red cell count, haemoglobin percentage, and haematocrit readings. Whereas the use of fluids such as normal saline or 5 per cent. glucose in normal saline when given parenterally (by subcutaneous or intravenous routes) caused a diminution in the concentration of the blood, it was found that the transfusion of whole blood caused an increase in blood concentration. In cases which in addition to being dehydrated were also toxic and in which blood transfusion would appear to be indicated, the use of plasma transfusion was suggested, and a small series of cases was treated in this way. In all cases the concentration of the blood was reduced, and in five cases out of eight immediate clinical improvement occurred, although all these infants were extremely ill. The suggestion was put forward that whenever possible the red cell count, haemoglobin estimation and haematocrit readings should be carried out in cases of dehydration in which the use of blood transfusion was considered, and in those cases which showed considerable concentration of the blood plasma should be used instead of whole blood.

12. Dr. R. C. Lightwood (London) : ' Dacryoadenitis : its occurrence in children and its clinical aspect.' Dacryoadenitis may be acute or chronic, unilateral or bilateral. Its etiology is much in dispute and in one-third of the reported cases the cause was undetermined. The literature is scanty. Primary infection causes bilateral involvement. Secondary cases may be due to general infections (bilateral) or ' neighbourhood ' infections (unilateral). Primary dacryoadenitis may be a disease sui generis and has been attributed to an unknown virus with specific affinity for the lachrymal glands, analogous with mumps. Secondary dacryoadenitis, also bilateral, has complicated many common infections, such as mumps, measles, scarlatina, tonsillitis, influenza, tuberculosis, syphilis and gonorrhoea. Among the

focal infections which have caused unilateral dacryoadenitis are furuncle, stye, dental abscess, nasal sinusitis and conjunctivitis. Two illustrative cases of bilateral type, seen by the author, were mentioned. One appeared to have been caused by continued tonsillar infection and was eventually relieved by tonsillectomy. The other was associated with benign pulmonary tuberculosis and may have been due to it. In such cases the clinical features are pain, orbital oedema, chemosis and slight constitutional disturbances. A bilateral orbital oedema with its greatest development in the outer part of the upper eyelid is characteristic ; and a ' satanic ' appearance may be caused through raising of the outer end of the eyebrows. The palpebral part of the lachrymal gland may be swollen and injected, and the orbital part may be felt by the finger. The differential diagnosis includes all causes of orbital oedema : stye, conjunctivitis, sinusitis, orbital cellulitis, cavernous sinus thrombosis, orbital osteitis, Quincke's oedema and nephritis. The prognosis is good, though a few cases persist for a long time.

13. Dr. W. R. F. Collis (Dublin) : ' Anal stenosis.' An extreme case was described in a child of seven weeks who had not passed a proper motion since birth. Obstruction, incomplete and of a membranous nature, was found 1½ inches above the anal sphincter. Recovery ensued after treatment including coloric lavage. Two types of anal stenosis appear to be described, one in which the stricture is found at the upper end of the rectum and the other with a stenosis of the anal sphincter itself. The case described belonged to the first group. The author described how in his work at the Rotunda Hospital Infant Clinic he had often met with cases of what he believed fell into the second group, of simple anal stenosis. The child was brought up by the mother for constipation ; on questioning, however, it was learnt that the motion when passed is not hard or dry but quite moist or even liquid. When the anal canal was examined digitally with the little finger the opening appeared small and the sphincter tight. No membrane beyond the anal sphincter is encountered. The digital examination stretches the sphincter and on withdrawal of the finger a motion, of moist or liquid consistency, is passed. One or two such stretchings appear sufficient to cure the condition.

14. Professor C. W. Vining (Leeds) : ' Faecal incontinence.' A group of children with this complaint were described. They were of school age and of normal mentality. The incontinence started after a period of normal control. There was a clear history of pronounced constipation since infancy in five of the children. Five of the cases presented themselves with palpable masses in the abdomen and in the case of two of the children the masses were sufficiently pronounced to stimulate an abdominal tumour. Films taken after barium enemata showed increased capaciousness of the pelvic colon and rectum as compared with control children. ' Follow through ' investigation showed delay in reaching the rectum and in final discharge. It was submitted that the incontinence was the final result of the previous retention and not due to congenital anomaly. It was thought that the constipation in the earlier years was produced on the usual lines, but there were possibly additional or accentuated factors which caused a more severe grade of constipation. All the children had been cured by the simple treatment of emptying the colon completely with enemata, this sometimes taking as long as a week, and following this by some simple laxative to give added stimulus. It was also necessary to explain to the child what was happening. There was a tendency for these children to prevent themselves having the bowel moved in their endeavours to prevent the incontinence.

15. Professor N. Morris (Glasgow) : ' The incidence of rickets in a large municipal hospital.' The incidence of rickets was investigated in 489 infants and children younger than three years admitted to the children's wards of a large municipal hospital (Stobhill, Glasgow). The tests for the presence of rickets were clinical, radiological and biochemical (high plasma phosphatase and low serum phosphorus). Of the patients 3·2 per cent. were sent in with diagnosis of rickets, while 49·1 per cent. had two or more signs of rickets. Of the last group the maximum incidence was found in the second year of life. A high plasma phosphatase was found in 49·8 per cent. of the cases ; the maximum incidence occurred in the first six months of life, the minimum in the third year. These findings indicate that the demand for calcium was in many patients greater than the amount retained, as a result of defective supply of lime or vitamin D or both.

16. Dr. W. W. Payne (London) : ' Some observations on bilious attack.' ' Bilious attack ' refers to the condition in which frequent attacks of vomiting, headache and abdominal pain occur. It is suggested that two stages in the attack occur—the first is due to oversecretion of adrenalin in response to fear, apprehension, excitement or fever. The adrenalin exerts its usual effects on the vascular system, such as pallor. It also affects the alimentary tract, causing relaxation of the gastric musculature and contraction of the pylorus ; similar relaxations and contraction occur in the small and large intestines, and may be the cause of

pain. As a result of the disturbance of the stomach, nausea is felt and vomiting may occur. Food taken may remain in the stomach for as long as twelve hours or more, producing a state of starvation. Again, adrenalin causes the glycogen stores of the liver to be dissipated and acetone bodies to be formed. This ends the first period. Spontaneous cure may occur. In other cases the second stage begins. This is the well-recognized stage of marked ketosis with its attendant symptoms, and occurs as a result of the carbohydrate waste and starvation of the first stage. It is more likely to occur when the carbohydrate stores are low before the attack. If vomiting has not occurred in the first stage the acute ketosis by enhancing the nausea will produce it now, and thus increase the starvation.

Treatment in the first stage consists in removing the anxiety, avoiding further overloading of the stomach and in stimulating its activity. The treatment in the second stage is similar, but sugar must be given. Prophylaxis in stage 1 is psychological, but the maintenance of good carbohydrate stores should lessen the likelihood of stage 2 occurring.

THE DETERMINATION OF GLUCOSE TOLERANCE

BY

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Historical introduction

One of the earliest examinations of the response of the human organism to the administration of sugar was made by Worm-Müller (1884), who published observations on the alimentary glycosuria of two healthy men. He found that these subjects, after being for some time on a diet very low in carbohydrate, showed a detectable glycosuria when given 50 gm. of glucose or sucrose or 100 gm. of lactose. This work was followed by that of Hofmeister (1889), who used dogs. His paper has the greater interest because it introduces the terms 'assimilation limit' and 'tolerance.' The former was used to imply the highest dose of sugar that the individual could take without showing glycosuria, while the latter was used, in speaking of certain diabetics of the milder type, to denote that dose a small increase upon which would produce glycosuria. Hofmeister did not, however, preserve any rigid distinction between the terms, and in fact, as Sansum and Wilder (1917) pointed out, what are really assimilation-limit determinations were for many years freely interpreted as showing limits of tolerance. He found that the assimilation limit for a given animal was constant, but that from one animal to another there was great variation. His work is also of importance at the present day for his clear recognition of 'hunger diabetes,' a phenomenon which Claude Bernard had encountered in dogs long before and which was, of course, implicit in Müller's work.

Seeking a measure of the assimilability of sugars, Linossier and Roque (1895) proposed the ratio $\frac{\text{sugar excreted}}{\text{sugar given}}$; but they obtained figures varying very widely even for the same sugar. Gilbert and Carnot (1898) showed a fairly constant ratio, however, lying between 40 per cent. and 100 per cent. when large doses (2·5–10 gm./kgm.) were given intravenously. Doyon and Dufourt (1901) found that the proportion of sugar excreted was largely dependent upon the time taken for administration, and following closely upon

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this work came that of Blumenthal (1905), who emphasized that the true conception of tolerance was not the static one, of a quantity which could be dealt with by each kgm. of tissue, but rather the dynamic one, of a quantity which could be so dealt with in each unit of time.

This fundamental idea made it necessary to have control of the rate of entry into the circulation ; and such control obviously demanded intravenous administration. It is a matter of some surprise that this point, made so very clear more than thirty years ago, has not yet been accorded its due weight in clinical practice.

Working on rabbits, Blumenthal found that a rapid injection of glucose amounting to about 0·85 gm./kgm. was tolerated without glycosuria ; but that if the dosage were either increased above this figure or repeated after too brief an interval, glycosuria occurred. He then approached an estimation of sugar tolerance as a velocity by establishing that a dose could be selected which, if given rapidly, could be repeated indefinitely at fifteen-minute intervals without the production of glycosuria. For rabbits, this dose lay between 0·6 and 1·2 gm./kgm.

Any method depending on the production of glycosuria must, as Maclean (1921) pointed out, be subject to a great source of error in the widely varying response of the kidneys to hyperglycaemia in different individuals and in different states of health and disease. For this reason, no great advance in clinical work on this subject was possible until Bang's publication (1913) of the first satisfactory method for the chemical estimation of blood sugar. This led at once to the great activity of the past twenty-five years, during which many workers have proposed tests of sugar tolerance based upon the estimation of the blood sugar after giving a test dose of sugar. The routes of administration have included the oral, the intravenous, and even the subcutaneous. The last is open to such obvious theoretical and practical criticism, however, particularly on the grounds of pain and sepsis, that it seems hardly necessary to consider it further.

General considerations

Before proceeding to discuss the oral and intravenous glucose tolerance tests, it will be convenient to consider certain factors of importance in the conduct of any test of tolerance, all concerned with the preparation and management of the patient and for the most part well recognized.

(*a*) **Rest.**—It was shown by Comessatti (1906), using Blumenthal's methods, that the tolerance of rabbits was improved by exercise in a treadmill, while Loeb and Stadler (1914) showed the converse to be true of resting rabbits. This result, subsequently fully confirmed in the human subject, indicates a difficulty in standardizing conditions. It is in practice satisfactory, however, that the patient remain in bed for the test after the preceding night's rest.

(*b*) **Preceding diet.**—Difficulties in this connexion were foreshadowed by Bang's recognition in 1913 that glucose tolerance was lowered by fasting and by Hamman and Hirschman's discovery (1919) that a second glucose tolerance curve was always lower than a shortly preceding one. These two observations

have been the inspiration of a vast amount of work, well summed up in Himsworth's comprehensive papers (1933–4–5). The conclusion emerges that the glucose tolerance of a healthy individual is directly proportional to, and is solely dependent upon, the amount of carbohydrate the diet has contained during the few days preceding the test. In practice, a patient whose tolerance is to be tested should, as far as possible, have taken a normal diet for three to five days. If that is not possible, it is important that the diet actually taken should be constant and well known, so that the results obtained may be adequately discounted. The importance of this matter may be gauged from the three oral glucose tolerance curves shown in fig. 1, which were derived from the same healthy child on normal, high-carbohydrate, and low-carbo-

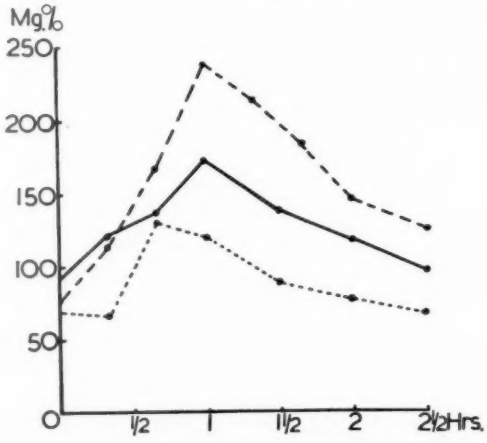

FIG. 1.—Three oral glucose tolerance curves (30 gm.) obtained from a normal boy on normal (solid line), low carbohydrate (dashed line) and high carbohydrate (dotted line) diets.

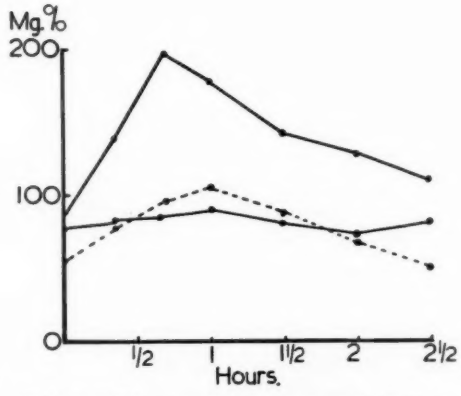

FIG. 2.—Dietary effects upon oral glucose tolerance curves. Upper curve (solid line) from a case of clinically occurring hunger diabetes, on admission with glycosuria. Dashed curve, from same case after a period on hospital diet with 50 gm. glucose added daily. The lower solid line shows the result of giving a normal boy 60 gm. of glucose daily in addition to ordinary diet.

hydrate diets. Two instances of extreme type are shown in fig. 2. The flat curve is the result of giving a normal boy of thirteen years 60 gm. of glucose daily, in addition to his normal diet, for several months. The high curve was obtained from an otherwise healthy boy of twelve years, who, by reason of unfortunate home conditions, was inadequately fed. It was rendered normal in form (dotted curve) by a period on hospital diet with 50 gm. of glucose added each day. This case was, in fact, one of 'hunger diabetes,' for the boy was sent to hospital for the investigation of an occasional glycosuria, which was never seen after the diet was corrected.

(*c*) **The period of fasting.**—The blood sugar normally shows fluctuations due to the intermittent intake of food (fig. 3), and obviously it would be confusing to conduct a test during the absorptive or immediate post-absorptive period. Hence, it is desirable to allow about five hours to elapse after a meal

before conducting a test. Further, as the distribution of carbohydrate among the three or more meals may be quite uneven, it is better still to carry out the test after the longer night fast, which serves excellently as a period of equilibration as well as standardizing the conditions with regard to exercise. Thus has arisen the usual and satisfactory practice of performing tolerance tests fairly early in the morning, the patient having fasted from the previous evening meal.

(*d*) **The emotional state** of the patient is of great importance, particularly in children. Pain or apprehension can easily lead to a rise of 50 mgm. per cent. or so in the blood-sugar level, and any procedure must be planned to exclude this factor as far as possible. The curve in fig. 4 shows the fasting blood-sugar level in a child of two-and-a-half years, who had a clean, granulating wound in need of dressing. The specimens up to 20 minutes were taken under normal conditions, after which the cot was wheeled into a dressing ward, causing the child to whimper apprehensively. The dressing was performed (it must have been practically painless) and the cot returned to its accustomed place. By

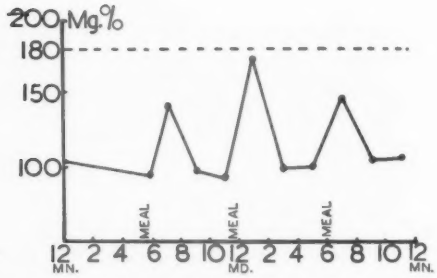

FIG. 3.—Diurnal variation of blood-sugar in a normal subject taking three meals daily, at 6 a.m., 12 noon, and 6 p.m.

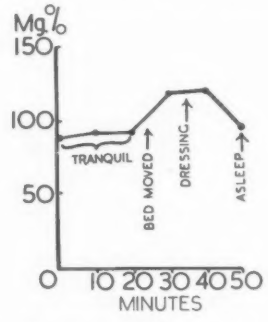

FIG. 4.—Fasting blood-sugar level of a child before, during and after emotional disturbance (see text).

45 minutes the child was asleep and the 50-minute specimen shows a return of the blood sugar to its previous level.

(*e*) **Infection.**—When it is not itself the subject of investigation, sepsis may produce disturbing effects upon tolerance curves. These effects have been so widely discussed as to call for no comment, beyond pointing out that even a heavy cold is sufficient to give a misleading result, especially in the case of the intravenous test.

Oral glucose tolerance tests (blood sampling)

The first observations of the blood sugar at intervals after the ingestion of a test dose were those of Bang (1913) and his co-workers. In the next few years a number of papers appeared dealing with such tests ; but the widespread use of the procedure, at least in the English-speaking countries, seems to date from the appearance of Maclean's method of estimating blood sugar (1919) and his well-known paper (1921) on the estimation of glucose tolerance. Since that time many technical variants have been employed, some of little importance, while others will be more conveniently discussed in dealing with special aspects of the test.

Dosage.—Great variation is found in the bases adopted by various workers.

Many use a fixed dose, while others vary it in proportion to the patient's weight. This variation according to weight (except in the widest sense) does not possess its apparent virtue ; for there can be little reason to think that equal weights of thin and obese, well and ill, normal and endocrinely disordered, active and inactive patients will be metabolically equivalent. Further, as Maclean (1921) pointed out, the hyperglycaemic effect of doses varying over a wide range is to

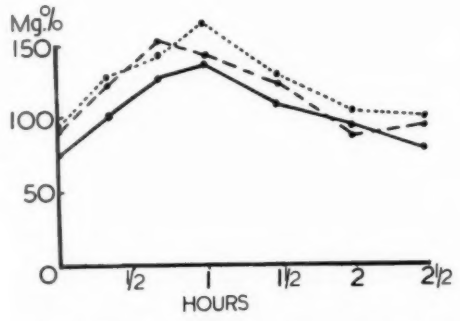

FIG. 5.—Oral glucose tolerance curves from three normal children using different doses of glucose, namely, 1 gm./kgm. (dotted line), 1·5 gm./kgm. (solid line) and 3 gm./kgm. (dashed line).

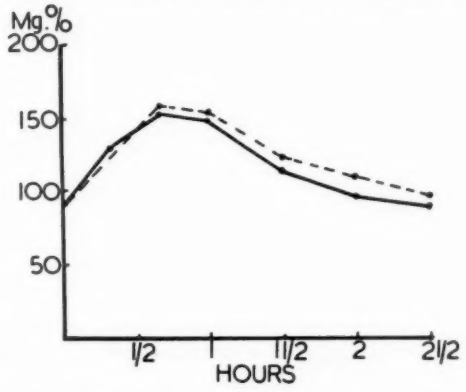

FIG. 6.—Two oral glucose tolerance curves derived from the same individual with doses of 1·4 gm./kgm. (solid line) and 2·8 gm./kgm. (dashed line).

all intents the same, except perhaps for some slight delay in the return to normal levels after a large dose. The curves in fig. 5 illustrate this in three different cases, while those in fig. 6 were obtained from the same case. It is interesting that excessive dosage tends apparently to delay the fall of the curve rather than to raise or advance its peak—a fact which is less surprising in view of the more

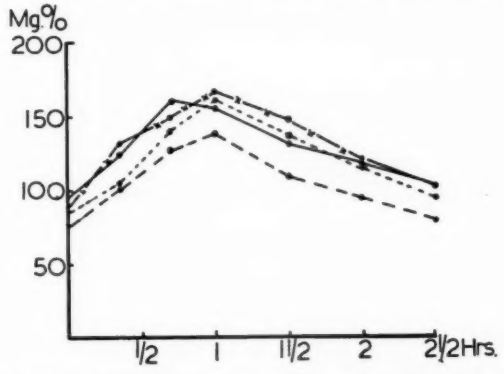

FIG. 7.—Four oral glucose tolerance curves from normal children, showing failure to return to fasting level in 2½ hrs.

modern knowledge of absorption and its complex nature. In many hands it has proved satisfactory to give 50 gm. for adults, while for children under 12 years a dose of 30 gm. has been used, reduced to 15 gm. if the weight is less than 10 kgm. This dosage tends to be high for small patients, and the fasting level is often not quite reached by two-and-a-half hours (fig. 7).

Strength of solutions.—This is an important point, for concentrations exceeding 25 per cent. are sometimes productive of nausea and erratic curves, while a large bulk of a rather unpalatable solution may even cause vomiting. The use of a 20 per cent. solution has usually provided a satisfactory compromise. The medium is, of course, flavoured water. Normal saline should not be used, for it markedly reduces the height of the curves (fig. 8), presumably by interference with absorption.

Frequency of sampling.—From the fact that elevation of the blood sugar usually begins within some five minutes of ingestion of the dose and reaches a peak after only twenty to sixty minutes, frequent sampling is desirable if an accurate conception of the early phases is to be obtained. In practice, there is some difficulty in collecting such large specimens as are ordinarily used, and half-hourly specimens are made to suffice. Intervals of twenty minutes during the first hour, and of half an hour thereafter, have been used in the present investigations. More frequent and yet accurately timed specimens are easily

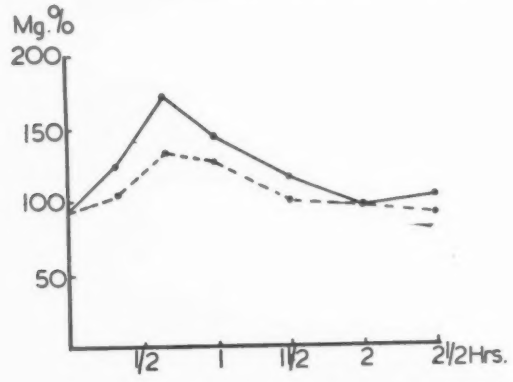

FIG. 8.—Two curves from the same normal patient, water (solid line) and normal (0·9 per cent.) saline (dashed line) being used as the solvent.

obtained, however, for estimation by the ultramicro method of Rappaport and Pistiner (1934) which will be described in some detail when the intravenous test is discussed.

Site of sampling.—The blood is usually obtained from a finger or ear-lobe puncture, though some workers, especially in America, use venous blood. Foster's work (1923) showed that the blood of the warmed pad of the dog's foot has practically the same sugar content as arterial blood ; and Goldschmidt and Light (1925) showed that blood taken from the veins of the warmed hand and from the arteries had an identical oxygen content. These two observations seem to justify the use of capillary blood, taken under good conditions, to represent arterial blood. Further, Himsworth (1933) checked the glucose content of blood from finger-pad and ear-lobe and found substantial agreement. Particularly in children the ear-lobe is the site of election, for small specimens at least. A satisfactory puncture made in this situation with a good Franck's lancet is practically painless and can be used repeatedly to obtain samples of 0·02 c.c.

The normal curve.—This is so well known as to require little or no description. It represents the changing resultant of two opposing influences, first, the tendency of the sugar entering by the portal vessels to raise the blood-sugar level, and secondly, the capacity of the body to remove sugar from the blood, thus tending to lower the level. The curve rises from a normal fasting value to a maximum, usually just below the renal threshold—say 150–170 mgm. per cent.—in half to one hour. Thence it falls in one-and-a-half to two-and-a-half hours to a few mgm. below the fasting level (unless the dose has been very large) to which it gradually returns (fig. 9, double line).

Grotesque curves.—Thus there are two aspects to the production of a normal curve—absorption into the blood and removal from it. It has been usual to

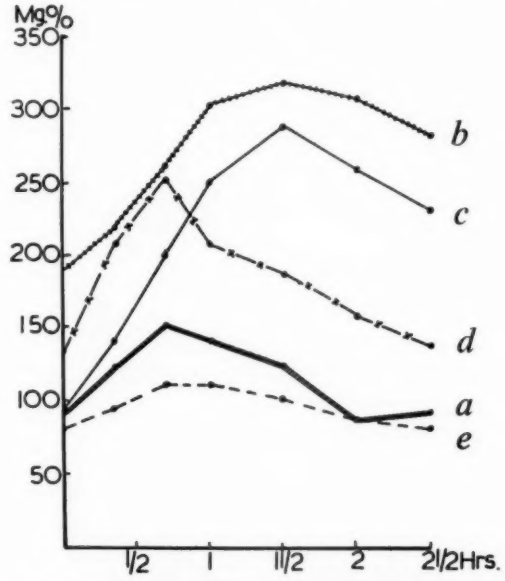

FIG. 9.—Some types of oral glucose tolerance curve : (*a*) normal (double line) ; (*b*) uncontrolled diabetic (+-+-+-+) ; (*c*) controlled diabetic (solid line) ; (*d*) 'lag' (×–×–×–×) ; (*e*) flat (dashed).

fix attention upon the latter rather to the exclusion of the former ; that this position is far from correct will be suggested by the latter part of this paper. Since there is no, or practically no, absorption of sugar from the stomach, the first requisite for efficient absorption is normal gastric emptying ; while the second is normal function of the small intestine as regards both motility and the actual process of absorption. From time to time a number of grotesque curves have appeared in the literature, either quite flat, or flat for a time and then rising to a great height, or bifid. Elsewhere (Ross, 1938) I have published a series of three such curves derived from one patient within a short period in which no clinical change occurred, with the suggestion that they are of gastric origin. Certainly such curves, unsupported by other methods of investigation, do not offer a safe basis for any conclusion regarding tolerance. They should rather be the indication for further investigation by other methods.

Abnormal curves.—These conform to three main types, two higher and one

lower than the normal. The former are the well-known ' diabetic ' and ' lag ' curves, the latter the ' flat ' type (fig. 9). The diabetic curve rises from an abnormally high fasting level, if the case is uncontrolled, or from a relatively normal one if insulin is being used, to a high level, whence it falls slowly and slightly. The lag curve rises from a normal or slightly high level to an unusual, often glycosuric, peak, and thence falls quite rapidly back to, or nearly to, the fasting level.

Both of these types have been accepted as indicating that sugar has entered the blood normally, but has been removed thence at an abnormally slow rate. In the lag curve this slow rate of removal has later been accelerated by stimulation of the body mechanism, by which pancreatic activity is usually implied. That pancreatic adjustment is a fact was classically demonstrated by Zuntz and la Barre (1927). But there is reason for doubting whether this is the only factor involved. Great interest has been taken in these curves for many years yet the number of reported cases in which the subjects have gone on to frank pancreatic diabetes is small. Much more usual is the experience of Hunt

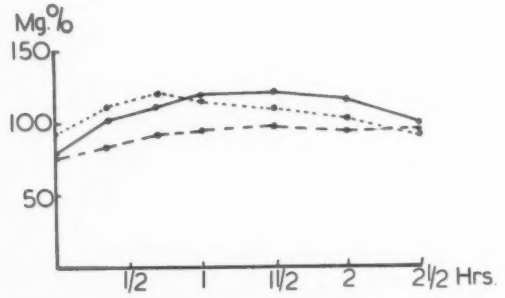

FIG. 10.—Three types of low oral glucose tolerance curve : (*a*) rounded type (solid line) ; (*b*) flat and non-falling type (dashed line) ; (*c*) low curve of normal form (dotted line).

(1937), no one of whose nineteen cases had returned in a ' diabetic ' condition. Further, dietary restriction can produce curves of this type (fig. 2), as also can sepsis and hepatic disease (unpublished cases). It is worth while to give every patient who shows a lag curve a high carbohydrate diet (say 300 gm. per diem for an adult), and repeat the test after a week. If then the curve is not normal or improved, the presence of liver disease or of some unobtrusive infection must be carefully considered.

Abnormally low curves have received, on the whole, much less attention. They fall, so far as they have been observed in this series, into three distinct types :

(*a*) A curve generally similar to the normal, but showing a smaller rise, often with a delayed peak or with no peak at all (fig. 10, solid line) and returning slowly to fasting level.

(*b*) Curves are occasionally found which approximate to a straight line, the blood-sugar level rising very slowly and very slightly and falling little, if at all, during two-and-a-half hours (fig. 10, dashed line). In the example shown, the maximal rise is 15 mgm. per cent. and the fall from this only 5 mgm. per cent.

Both of these types have been seen in conditions of impaired absorption (Ross, 1935, *a*, *b*).

(*c*) The last type of ' flat ' curve is seen, in contrast to the two already mentioned, in patients whose tolerance is excessive. In this type a small rise is followed by a greater fall, with later restitution (fig. 10, dotted line ; fig. 2, lower solid line).

Obviously, accurate interpretation of these low curves is not possible without further information than the curves themselves provide ; for they could result from failure of glucose to reach the intestine (gastric stasis), failure of absorption (disease states or acute intestinal hurry), or unduly rapid removal of sugar from the blood (hypertolerance). The first of these fallacies has been freely discounted, especially since Maclean's opinion was given (1921) that absorptive

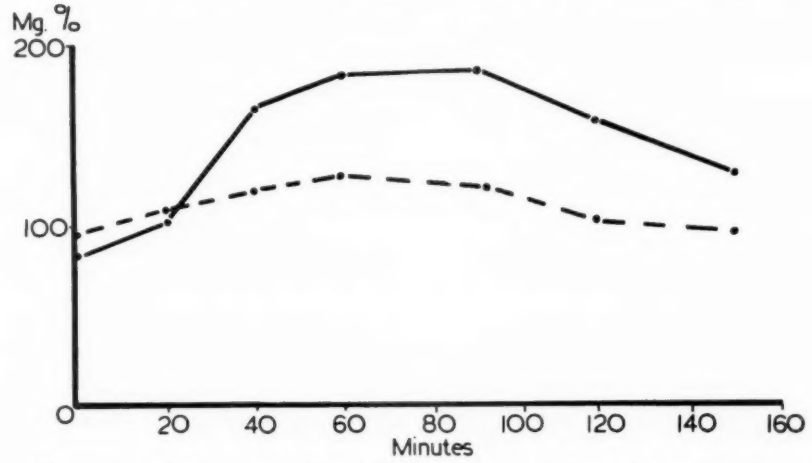

FIG. 11.—Two curves from a case of coeliac disease : (*a*) early in the period of onset (solid line)—a high curve ; (*b*) at a more advanced stage (six weeks later), with definite symptoms (dashed line)—a flat curve.

irregularities were not likely to influence results significantly. Later work, however, does not support that view.

A further difficulty exists, to which attention has previously been drawn (Ross, 1935, *b*). This is the ambiguous character of the ' normal curve.' As has been seen, this curve results from the absorption of sugar followed by its removal at a rate indicative of the individual's ' tolerance.' Now, when absorption is impaired, less sugar will enter the blood (tending to give a lower curve) ; but on the other hand, the glucose-tolerance will be impaired (for bad absorption must have the same effect as carbohydrate deprivation, and it is known (Himsworth, 1935) that this leads to impaired tolerance). Hence there is one factor making for a low curve, another for a high one. The actual resultant depends merely on the degree and duration of the absorptive disability. It is for this reason that cases of absorptive disease (e.g. coeliac disease and abdominal tuberculosis) are found which show almost normal oral curves, although the intravenous test shows their tolerance to be grossly impaired. An opportunity was afforded of watching one child during the development of coeliac disease. At an early stage, when there was no symptom of note beyond

listlessness and failure to gain weight, a fairly high curve (solid line, fig. 11) was obtained. Some six weeks later, when the condition was definitely established, a flat curve was found (dashed line). The reverse sequence of events has been noted by Fairley (1936) during the cure of sprue. Patients who have shown flat curves during the acute stage, on partial recovery show high ones, which then subside to normal when health is fully restored.

It will be seen, therefore, that when a ' lag ' or a ' diabetic ' curve is obtained, the oral test may be taken as sufficiently accurate for practical purposes. But when in the presence of symptoms low or normal curves are found, it is necessary to turn to other methods, and particularly the intravenous glucose tolerance test, for elucidation.

Two-dose tests and other such variants will not be discussed here, for although they are by no means without significance, they are in theory more closely germane to another paper which is in preparation.

The intravenous glucose tolerance test

The first study of the injection of sugar into the veins which has been discovered is that by F. J. von Becker (1854), who observed the glycosuria produced in rabbits by this means. Clinical use was not made of this route, apparently, until 1913, when Thannhauser and Pfitzer published some curves obtained by giving injections of 7 per cent. glucose solution, and observing the course of the blood sugar. They had to give a large volume of solution, usually some 500 c.c., and hence took fifteen minutes to make the injection. In 1915 Woodyatt, Sansum and Wilder felt the necessity of eliminating the unknown absorptive factor by using the intravenous route ; but they also sought to avoid the ' wave ' effects of Blumenthal's technique—to apply a perfectly even stress to the sugar-removing mechanism. They therefore devised a finely-regulable motor-pump capable of delivering a continuous and positively governed flow.

As normal subjects they used only healthy persons from twenty to forty-five years of age, in an average state of nutrition, who had been on a mixed general diet. On the day of the test no food was given, and injection commenced at 2–4 p.m. The initial rate of 0·7 gm./kgm./hr. was increased slightly each twenty to thirty minutes until glycosuria appeared. The normal tolerance rate thus determined was found to lie between 0·8 and 0·9 gm./kgm./hr.

This continuous method, however, is quite unsuited to clinical practice, and, like earlier and far cruder tests, it still embodied the unknown factor of renal function. Further, the test itself must have had the same effect as a high carbohydrate diet in influencing the tolerance as finally determined, i.e. it could not easily reveal impairment of tolerance due to acute dietary privation. Conversely, of course, it had the virtue of eliminating to some extent errors due to diet when other influences were being investigated.

It is not surprising, then, that later methods have nearly always been modifications of that of Thannhauser and Pfitzer (1913), an injection of glucose solution being given fairly rapidly and the blood sugar being estimated immediately before and at stated intervals after the injection.

Some twenty-three of the early tests having been reviewed by McKean, Myers and von der Heide (1935), it is not necessary to recapitulate them in detail. The points in which variation has occurred, however, are dosage, strength of solution, time of injection, frequency of sampling, duration of observation and the actual method of estimation of blood sugar ; and each of these calls for some discussion.

Dosage.—The same arguments have been advanced for graded dosage in this test as in the oral one ; and much the same objections lie. It is obviously necessary to select a dose which will be safe and yet adequate to stress the sugar-removing machinery. Sansum and Wilder's figure gives an indication

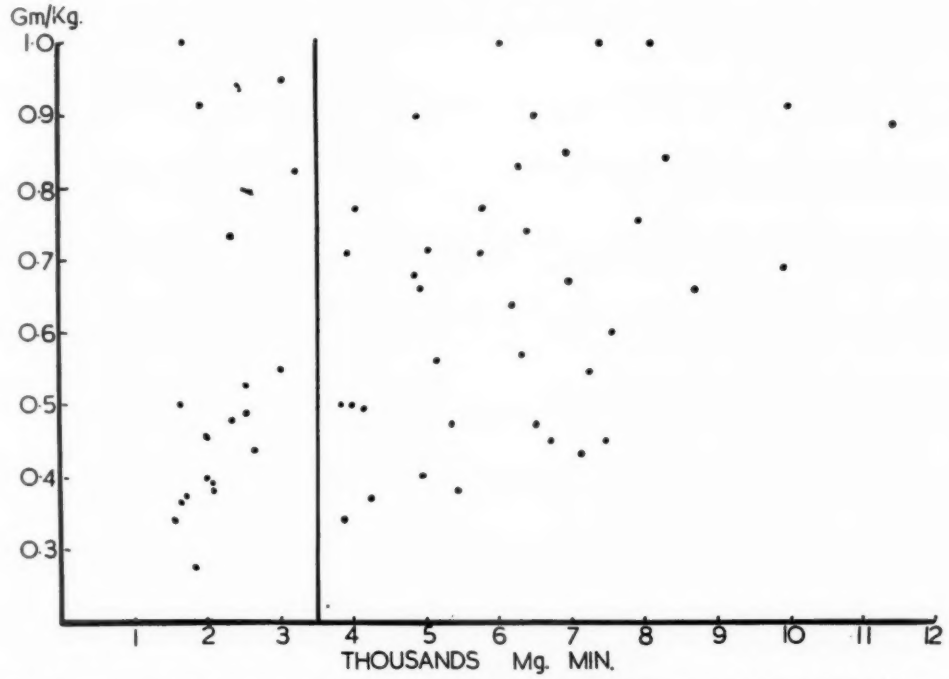

FIG. 12.—Showing the areas of intravenous glucose tolerance curves obtained in health and disease using varying dosages of glucose. All points to the left of the vertical line (under 3,500 mgm. minutes) were derived from normal cases ; all those to the right are from cases of disease taken at random from various groups—coeliac disease, abdominal tuberculosis, liver disease (acute and chronic).

of what such a dose might be for a test designed to last about an hour—namely, something less than 1 gm./kgm. Jorgensen and Plum (1922) used a 20-gm. dose with considerable success. Hence in beginning work on children, I tried doses of 5 gm. up to 10 kgm., 10 gm. up to 30 kgm., and 20 gm. for bigger children or adults. This grading of dose was not intended in any sense to give a strict approximation to a weight basis, but merely to render the injections safe and convenient. That such an arbitrary method was justified is shown by fig. 12. This is designed to show the influence of dosage upon curves obtained from normal and abnormal subjects. The intravenous glucose tolerance curves are measured as shown in fig. 13 by means of a planimeter. The area measured is bounded by a vertical line at two minutes, the horizontal through

the fasting level, and the curve itself, with if necessary a vertical at sixty minutes to join the curve to the horizontal when they have not met. The areas so measured are expressed in mgm. mins.—i.e. the product of the mean elevation of blood sugar above fasting-level in mgm. per cent., and the time in minutes for which it persisted (up to one hour). This method of measurement is not intended to confer upon tolerance curves the suggestion of an accuracy which they inherently lack, but merely to render easier a comparison, in terms of tolerance, of curves differing in form. It will be seen from a study of fig. 12 that in normal subjects there is little dispersion of the tolerance areas with variation in dose, though in the abnormal cases there is some tendency to this. In fact, there is here a suggestion of Allen's famous ' paradoxical law '—the limits of tolerance in the normal cases (and within the limits of dosage shown)

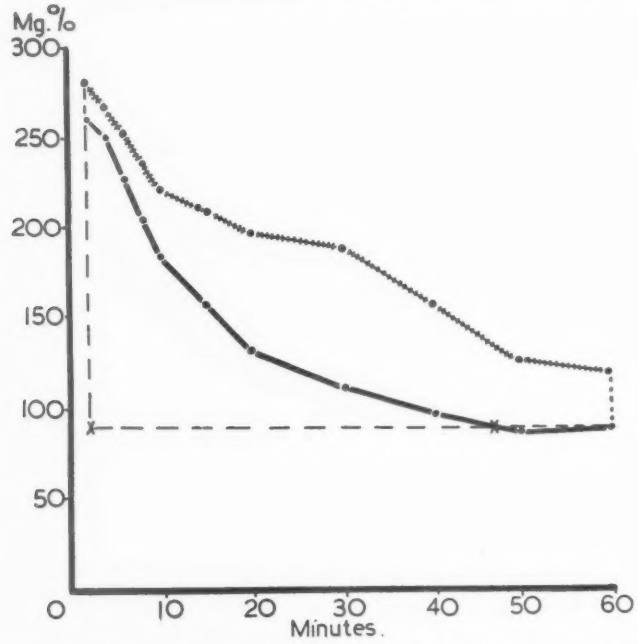

FIG. 13.—Showing the mode of measuring intravenous glucose tolerance curves (see text).

seem to be virtual only ; while in the abnormal they tend to be actual. The possibility of producing such a diagram seems to dispose of any need for close standardization of dosage. Fig. 14 shows two actual normal curves obtained from different subjects with widely differing dosage (0·38 and 0·95 gm./kgm. respectively), while the two curves in fig. 15 were obtained from the same normal child using 0·5 gm. and 1 gm. per kgm. It will be seen that the curves are a little irregular, and this may be attributed to the child's extreme nervousness.

Strength of solution.—Since there is a definite limit to the speed with which fluid can safely be put into the veins, it is necessary to keep the volume of the test-dose low if rapid injection is to be made. On the other hand, concentrated solutions are not without danger, and, even short of serious mishap, may occasionally cause considerable, if temporary, vasomotor disturbance, as seen in alternate flushing and blanching of the face and neck. The compromise of

using 20 per cent. solutions in normal saline has been successful, in that the appropriate dose can usually be given in one minute, always in two minutes, and vasomotor disturbance is rarely seen. Normal saline is the only solvent

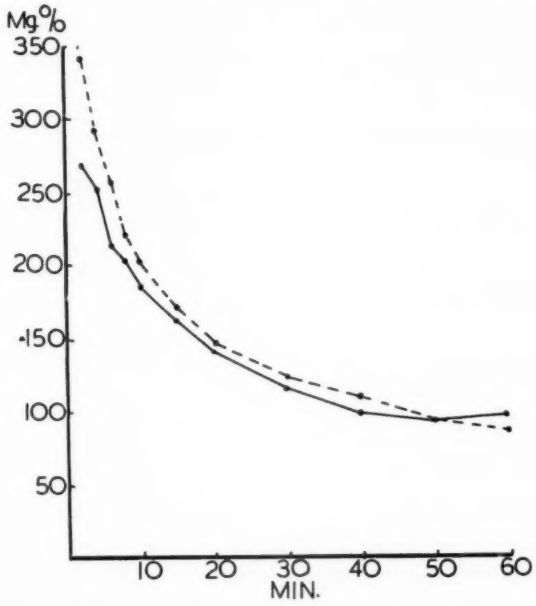

FIG. 14.—Two normal intravenous glucose tolerance curves, obtained with widely varying dosage : (*a*) 0·38 gm./kgm. (solid line) ; (*b*) 0·75 gm./kgm. (dashed line). These curves are from two different subjects.

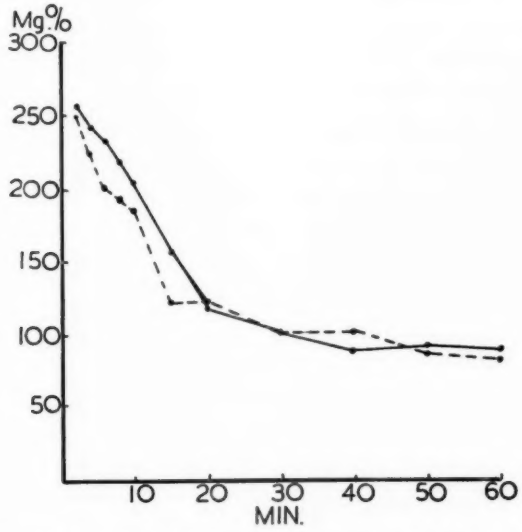

FIG. 15.—Two intravenous glucose tolerance curves obtained by giving 5 gm. (0·5 gm./kgm., dashed line) and 10 gm. (1 gm./kgm., solid line) of glucose to a normal child.

employed. It is well to point out that Crawford's statement (1938*a*) that water was used has since been corrected (1938*b*). In many hundreds of such injections there has been no mishap.

Purity and sterility are essential in the preparation of solutions. Use has been made of glucose fulfilling the requirements of the U.S.P. X, analytical reagent standard sodium chloride and water twice distilled over glass. The solutions were finally autoclaved in their plugged flasks. Under these conditions, there have been no reactions whatsoever.

The injection.—As has already been seen, this must be accomplished painlessly and without emotional disturbance of any kind. In dealing with children it is therefore necessary to gain the patient's confidence and to have skilled nursing assistance, A fasting specimen having been taken, the skin overlying a suitable vein is carefully anæsthetized and the vein exposed through a small oblique incision. A graduated funnel, rubber tubing and cannula are employed a little normal saline being run in to prove that the flow is free. The appropriate dose of glucose solution is evenly run in, due allowance being made for the dead space between the zero mark on the funnel and the vein. It may at first be thought impossible to achieve all this without disturbing the patient ; but with care and use the procedure is quite practicable. Control injections of normal saline alone have been made, and it was found that the incidental variation in blood sugar is not more than about ± 10 mgm. per cent. and over a period of a few minutes only. In children and nervous adults a needle method should not be used unless the vein is so large that a local anæsthetic can be employed without prejudicing the success of the injection. By the use of this simple gravitational method, with full visibility, it is not difficult to make the injection at a fairly steady rate and in a suitable time.

Time of injections.—Since the object of the test is to observe the ability of the body to remove sugar from the blood, it is theoretically desirable to create instantly a state of maximal hyperglycaemia. This, of course, is not practicable, but with the dosages and solutions mentioned it is usually possible to observe a standard injection time of one minute, which gives a fair approximation to this. It is probably unimportant if perchance the injection takes as long as two or even four minutes ; but longer periods—of ten or fifteen minutes—may lead to difficulty in interpreting certain ' humped ' types of curve (to be described later), even if these are ever seen in such circumstances. It is, perhaps, desirable to make it very clear that feats of rapid injection, which are highly dangerous and never necessary, are not advocated.

Frequency of sampling.—The hyperglycaemia produced by the injection is usually maximal at once, and there follows a more or less rapid fall, the fasting level being attained in about one hour. It is therefore necessary to collect specimens at short intervals during the first part of the curve, in order to follow the rapid changes adequately. For this reason, specimens have been taken at 2, 4, 6, 8, 10, 15, 20, 30, 40, 50 and 60 minutes after the injection. In point of fact, as will emerge from what follows, such frequent sampling is unnecessary for diagnostic work of the ordinary kind when familiarity with the test has been attained.

Duration of observation.—With the test described, this should be about one hour—more perhaps as a matter of interest—since in the normal case the fasting level is re-attained at about one hour. A further half hour will be

necessary if it is desired to place emphasis on the time taken to return to fasting level ; but that point is probably less significant than the area and form of the curve.

Blood-sugar estimation.—It is not proposed here to discuss the relative merits of the various well-known methods of estimating the blood sugar, but to draw attention to the excellent ultramicro method—using only 0·02 c.c.—described by Rappaport and Pistiner (1934). Some such method is desirable in view of the necessity for small and accurately timed specimens in the intravenous test. As the original publication was made in German and in a journal which is not very generally available except to specialists, it will be useful briefly to recapitulate it, giving only such detail as is practically necessary.

The method is an adaptation of the ferricyanide reduction method of Hagedorn and Jensen. The specimen (0·02 c.c.) is conveniently collected in a Haldane haemoglobinometer pipette, and is immediately expelled (the pipette being washed out three times) into 1 c.c. of N/50 sodium hydroxide, freshly prepared by diluting 0·8 c.c. of 10 per cent. solution to 100 c.c. After thorough mixing, 1 c.c. of 0·45 per cent. zinc sulphate (made by recent dilution of a 22·5 per cent. solution) is added, and the tube is again agitated. As soon as possible after conclusion of the test, the tubes are boiled for three minutes in a water-bath, together with blanks of the two reagents alone. The specimens and blanks are now carefully filtered through a small wad of cotton-wool of a fine grade, washed thoroughly before and after with hot distilled water, the wool being finally pressed out with a glass rod. The filtrate should be crystal clear. To each tube is added exactly 2 c.c. of buffered ferricyanide solution. This solution consists of two parts, mixed in equal volume immediately before use. These are: (i) 0·9 gm. potassium ferricyanide made up to 1 litre with distilled water ; (ii) 21·0 gm. anhydrous dipotassium-hydrogen-phosphate and 63·75 gm. anhydrous tripotassium-phosphate dissolved in distilled water and made up to 1 litre. After addition of the ferricyanide solution, the tubes are placed in a boiling water-bath for exactly twenty minutes, and then thoroughly cooled. To each is added 1 c.c. of zinc-sulphate–potassium-iodide reagent (recently prepared by adding to a 20 per cent. sulphate solution sufficient solid potassium-iodide to give a concentration of 2·5 per cent. in the mixture) and 1 c.c. of 20 per cent. phosphoric acid (20 c.c. of syrupy acid, s.g. 1·75, made up to 100 c.c. with distilled water). A drop of starch indicator (0·5 per cent.) is added, and specimens and blanks are titrated with N/1000 thiosulphate solution, preferably from a 3 c.c. microburette calibrated in 0·01 c.c. and having a fine tip. The thiosulphate solution is made by diluting 10 c.c. N/10 sodium thiosulphate and 12 c.c. N/1 sodium hydroxide to 1 litre. This solution should be frequently standardized by titration against a N/1000 potassium dichromate or potassium iodate solution. As the end-point is reached vigorous shaking is advisable to be sure of a sharp reading.

The reactions involved are as follows. The filtrate is heated in alkaline solution with a measured amount of ferricyanide, some of which is reduced by the glucose to ferrocyanide. With the zinc-sulphate–potassium-iodide reagent in an acid medium, the excess ferricyanide liberates iodine :

$$2K_3Fe(CN)_6+2KI\rightarrow 2K_4Fe(CN)_6+I_2,$$

while the ferrocyanide is precipitated as the double potassium-zinc salt :

$$2K_4Fe(CN)_6+3ZnSO_4\rightarrow K_2Zn_3(Fe(CN)_6)_2+3K_2SO_4.$$

The difference between the thiosulphate required to titrate the iodine liberated

in the blank and in the unknown is a measure of the glucose present. By experiment a factor is found which will convert this difference into terms of mgm. per cent. This was found to average 174. The glucose value of the unknown is therefore : 174 × (c.c. of thiosulphate for blank − c.c. for specimen). The specimens are stable after the addition of the zinc sulphate until the ferricyanide is added, and in practice if there must be some delay in completing the estimation it is best to allow this to occur after the zinc-sulphate has been added. In duplicate estimations the results obtained coincide with those obtained by the Hagedorn-Jensen method within 1 mgm. per cent.

The normal intravenous curve

Two typical normal curves are shown in fig. 14 (solid line). It will be seen that, from a peak which is far above the normal renal threshold, the curve of descent (when plotted so that 50 mgm. on the ordinate corresponds to 10 minutes on the abscissa) approximates to a parabola, the blood sugar falling much more rapidly at first than in the later stages. The normal level is attained in fifty to sixty minutes, and there may be a slight following hypoglycaemia. The height of the peak is of little significance, for it must depend upon dosage per litre of blood, rate of injection in relation to both blood volume and dose, and perhaps other factors less obvious. The essential feature is the steady fall, of initially high rate, in an unbroken curve. Occasionally bifid peaks have been encountered. The meaning of these is by no means clear, unless they reflect vasomotor or emotional disturbance. Minor irregularities are found in the curve whenever the patient is emotionally disturbed ; and not unnaturally these are seen most often in cases of coeliac disease and allied disorders, in young children and in nervous adults.

It is not considered desirable to publish a suggested standard of normality for this test, as investigation of a large enough number of truly normal subjects for the purpose has not been possible. Certainly, it is not safe to assume the normality of convalescents. Sheldon (1938) and Crawford (1938*a*) have both. recently published curves of this kind which cannot be accepted as normal. This test is a much more delicate instrument than the oral one, and any trace of infection (even a coryza), a recent period of light diet, or a major anæsthetic given even two weeks previously may lead to definite shortcomings in the curve of an otherwise normal subject. However, it can be stated with confidence that three definite criteria are met by the normal curve :

(*a*) In form it is a smooth, hollow curve, resembling a parabola, when plotted as described above.

(*b*) It attains the fasting-level, or comes within about 20 mgm. per cent. of it, within one hour.

(*c*) Within the limits of present experience, its area does not exceed 3,500 mgm. minutes when measured as described above.

Abnormal curves

These may be divided into a large group of curves in which the area is greater than normal ; and a small one in which it is less. The former are,

of course, all indicative of impaired tolerance, but they conform to three main types :

(*a*) The ' diabetic.' This is the homologue of the diabetic oral curve. It rises from a normal or high (if uncontrolled) fasting level to a great height, whence it falls slowly and very slightly (fig. 16, solid line).

(*b*) A common type, in which the normal curve is replaced by a flat curve approaching at times a straight line, usually remaining above the fasting level at one hour (fig. 16, dotted lines). Varying degrees of this type are seen, and four are shown. These curves are found in a variety of conditions, including

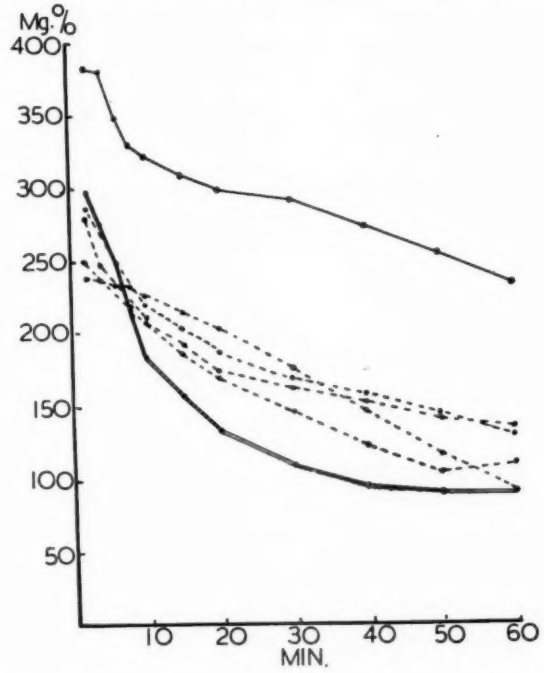

FIG. 16.—High (abnormal) intravenous glucose tolerance curves, contrasted with a normal (double line) : (*a*) diabetic (solid line) ; (*b*) non-diabetic impairment of tolerance (see text) (dotted lines).

carbohydrate deprivation and impaired absorption, intoxication, infection, and liver disease.

(*c*) The ' humped ' curve (fig. 17, dashed lines). Here there is a more or less rapid change in the rate of fall of the blood sugar at from twenty to fifty minutes, usually about thirty minutes, the curve becoming convex. This striking type is seen at times in carbohydrate deprivation and in absorptive disease or disorder.

Curves of a smaller area than normal are uncommon and we have seen them in only four conditions—in the normal subject after high carbohydrate diet (fig. 18, solid line) ; in Frohlich's syndrome, when the curve is sometimes similar; in a case of suprarenal neuroblastoma, in which the fasting level was high but the tolerance great, presumably from hyper-adrenalinism (dashed line) ; and in a case of hepatomegaly thought to be due to compensatory hypertrophy after subacute necrosis (dotted line). In this connexion it is

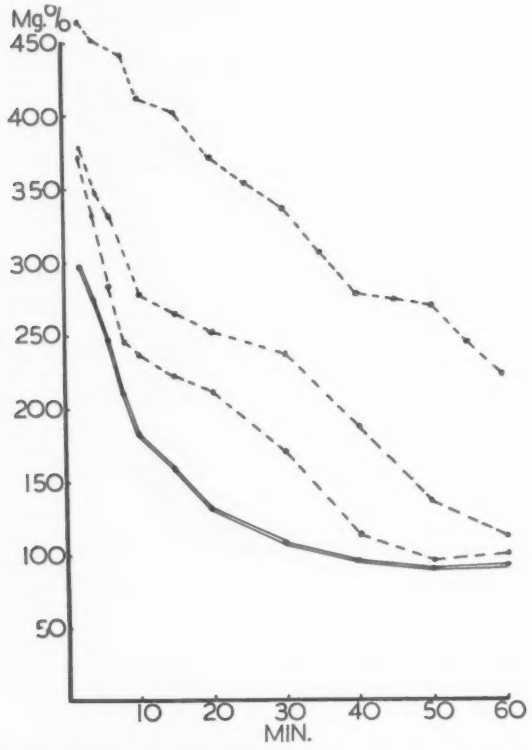

FIG. 17.—' Humped ' (abnormal) intravenous glucose tolerance curves, contrasted with a normal (double line).

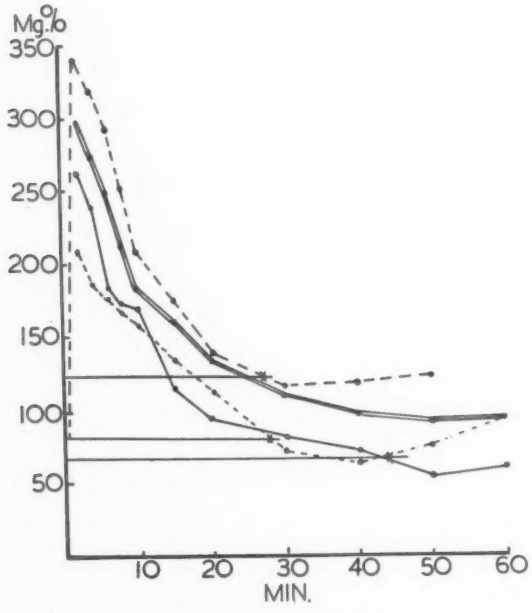

FIG. 18.—Abnormally low intravenous curves contrasted with a normal (double line) : (*a*) high-carbohydrate diet in a normal subject (solid line) ; (*b*) suprarenal tumour (dashed line) ; (*c*) hepatomegaly (?) hypertrophic (dotted line).

interesting to note the statement in Crawford's paper (1938*a*) that there is a gradual prolongation of tolerance curves in children as the age increases. It is possible that this merely reflects the tendency of younger children to take a higher carbohydrate diet. Curves performed with patients on standard ward diet reveal no such tendency.

The interpretation of intravenous curves is a relatively simple matter, for they represent only one process—the removal of sugar from the blood. Admittedly, while the blood-sugar level is above renal threshold there may be, and there sometimes is, a glycuretic contribution to this ; but the later portion of the curve represents ' tolerance ' alone, and this is at once shown as normal, subnormal, or supernormal.

The only type of curve calling in itself for further comment is the ' humped ' variety. Here there is patently a change of tolerance during the test, and the implication is that that change is due to the test dose. It probably represents, in fact, a sensitization of insulin, and is of the same general nature as the ' Staub-Traugott phenomenon ' (Himsworth, 1933–4–5). It is of some interest that this type of curve has been seen only in the relatively less chronic conditions of starvation or malabsorption.

The combination of oral and intravenous tests

This combination is of particular interest, in that it gives information regarding absorption which is not available from either source alone. In fact, apart from symptomatology, it provides the first method available of demonstrating a deficient absorption of digested carbohydrate, since the quantitative analysis of faeces for carbohydrate residues is not practicable. In the following table there are summarized the findings made by using both tests in a variety of conditions.

TYPE OF CONDITION	CLINICAL INSTANCES	ORAL CURVE	INTRAVENOUS CURVE
Hypoinsulinism ..	Diabetes mellitus.	' Diabetic.'	' Diabetic.'
Carbohydrate deprivation.	Starvation.[1] Anorexia nervosa.[2] Experimental diets.[3]	High with delayed fall or typical ' lag.'	High with delayed fall ; may be ' humped.'
Deficient absorption of carbohydrate.	Coeliac disease.[4] Sprue.[5] Chr. idiop. steatorrhoea.[6] Mesenteric tuberculosis.[7] Chr. intestinal dyspepsia.[8]	' Flat.'	High ; may be ' humped ' in some.
Infection. Intoxication.	Tonsillitis, arthritis, etc.[9] Diphtheria.[10] Alcoholism.[11]	High.	High.
Liver disease ..	All grades, acute and chronic, from catarrhal jaundice to cirrhosis and necrosis, except post-necrotic hypertrophy.[12]	High, unless gross intestinal disturbance, when it may be flat or grotesque.	High ' flat ' type.

[1] See fig. 2. [2] Ross, 1938. [3] See fig. 1. [4] Ross, 1936*a*. [5] Fairley, 1936. [6] Vaughan, 1936. [7] Ross, 1936*b*. [8] Ross, 1936*c*. [9] Pemberton, 1920. [10] Begg and Harries, 1935. [11] Unpublished cases. [12] Jacobi, 1936–7 ; Ross, 1936*a*.

It will be seen that, with the aid of the combined tests, defective absorption may be detected. If insulin-sensitivity is also measured, diabetes mellitus can with certainty be separated from other common conditions giving a high intravenous and oral curve.

Summary

(1) The history of tolerance investigations is briefly reviewed.

(2) General considerations affecting any test of tolerance are considered.

(3) Oral tolerance tests are discussed, with special consideration of ' flat ' curves and their significance.

(4) Intravenous tests are considered in detail, and a technical description is given.

(5) Intravenous curves are described and their significance indicated.

(6) The use of combined oral and intravenous tests is indicated, particularly in the demonstration of defective absorption.

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PERIPHERAL BRACHIAL PARALYSIS IN INFANTS AND CHILDREN *

BY

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In 1861 Duchenne noted in four cases of ' subacromial subluxation,' thought to be produced at birth, a true paralysis of the brachial plexus. In 1872 he described in detail obstetrical paralysis, with or without fracture or subluxation, and in older children described subspinous luxation as complicating or producing the paralysis (Duchenne, 1872). Erb, in 1874, localized by faradic stimulation an area in the neck associated with the contraction of the muscles most commonly paralysed in this lesion. This point was later associated with lesions at the junction of the fifth and sixth cervical roots (reviews by Williamson, 1897 ; Kennedy, 1903). Whereas the earlier observers blamed direct pressure from forceps, the midwife's finger or the subject's clavicle, the work of Fieux and more especially Duval and Guillain towards the end of the last century emphasized traction on and rupture of the upper roots of the plexus from forcible separation of the head and shoulder. Much experimental work on the cadaver has supported this view (Delbet and Cauchoix, 1910 ; Sever, 1920 ; Taylor, 1921). Whitman (1905) by his work on reduction of the subluxation sometimes present emphasized this aspect, and several workers have followed T. Turner Thomas (1911) in regarding the subluxation as primary in some cases at least (Ashhurst, 1918 ; Lange, quoted from Thomas, 1916 ; and Platt, 1921).

Case records

The relevant cases attending the Belfast Hospital for Sick Children for the past six years have been investigated. These twenty-nine cases, which include three post-natal traumatic lesions, are entirely unselected and may be considered quite representative. Though the number of cases is small a study of the literature suggests that it falls to the lot of few to examine a large number Fairbank (1913) reported forty cases, Froelich (1921) and Gilmour (1925) each encountered twenty-five cases, and McFadden (1928) studied fifteen cases. Sever (1925) of Boston has, however, collected data of eleven hundred cases. An analysis of this material illustrates the almost infinite variation which may be met with in the evolution of this type of lesion, and how artificial is any attempt to describe the later development of these children in a few general classes, however similar many may appear when first presented. A summary of a number of selected cases will illustrate the variation in recovery and function attained.

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Case 1. A full-time female child was born as a vertex to a primipara after a twelve-hour labour with anaesthesia and instruments. The child showed no asphyxia and no bruising. When first seen at the age of three weeks she showed a right-sided sterno-mastoid swelling, which increased for a few weeks, but gradually disappeared. The right arm hung vertically from the shoulder, internally rotated, fully extended and pronated at elbow. There was no carpal deviation, no definite wrist drop and, though the digital muscles appeared normal, the fingers were flexed and thumb adducted (fig. 1). There was no tenderness and no resistance to passive movement. The most powerful displacing forces were the pectoralis major and the latissimus dorsi muscles. The

FIG. 1.—The earliest position of the limb.

paralysed muscles were those typically involved in the upper arm type of birth palsy.

Treatment by a right angle abduction splint relaxed the paralysed muscles and movements and light massage were given. After three months supination at the elbow was slightly better and wrist drop could be definitely excluded, the humeral head was very mobile and there was slight wasting of the deltoid, spinati and elbow flexors, but no contractures in the active muscles. After five months the elbow flexors, though weak, had recovered some power. As evidence of recovery in the shoulder muscles the deltoid was beginning to ' fix ' the shoulder for abduction by scapular movement. Six months later recovery was still incomplete at the shoulder, but no contractures had developed.

This patient was treated early with delay in recovery. The value of treatment is shown by the control exercised on the development of contractures. Another similar example was seen showing better, but not complete, recovery after six months.

Case 2. This was a female infant, a fifth child, since followed by four normal children, all easy births. She was a large full-time child born under anaesthesia as a breech five to six hours after rupture of membranes. The obstetrician thought he heard something give a crack during delivery. No other injuries were noted, but the baby was difficult to resuscitate. The left arm and forearm hung limp from birth, the wrist and hand were normal. The infant was treated for six weeks from first week by fixation of arm behind head by collar and cuff and without massage. Some improvement was noted in three weeks. The baby started to move whole arm in six weeks.

On examination at age of five years she is a healthy, well-developed child. Shoulder and arm are perfectly normal in appearance. The arm swings spontaneously when walking. All passive and active movements are full. When abducting the arm from the side movement starts in the deltoid arc ; after about 45° abduction the inferior angle of the scapula, which has remained relatively steady, glides outwards. Range and strength of abduction and external rotation are equal on both sides.

Five other similar cases were observed. Two, treated with arm in sling in front of body, a bad position, showed complete recovery, as did a case treated by massage only.

Case 3. A first child, a female, was born as a vertex with instruments after thirty-six hours. There was much difficulty in delivery of shoulders and later in starting respiration. The ear and face were cut and a right sternomastoid tumour developed later. In addition to typical position of the arm, the right scapula was always prominent. She was treated from fifth week by fixation of hand by bandage behind head in correct position to relax all paralysed muscles, and from sixth to fifteenth month in an aeroplane splint. Slight recovery was noted at eighth week and shoulder abduction at seventh month.

When examined at age of two years she showed slight prominence of both scapulae at rest, and marked winging of right when arm abducted, especially when pushing against resistance. The right arm could be elevated just above the horizontal (right serratus magnus weakness, not paralysis). Deltoid recovery was good, and external rotation fair. The hand in a useful supinated position could reach the mouth. The arm was used well and there was no wasting nor shortening.

X-RAY : Bony outlines normal. Normal diaphragmatic level.

This patient is recovering satisfactorily, and without disabling contractures. Serratus magnus paralysis is present, but now only residual.

Case 4. After an instrumental delivery a female infant, said to weigh 14 lb., was born to a multipara five hours after rupture of the membranes. The right arm hung limp, but fingers and hand could be moved from the beginning and there were no other birth injuries. She was treated for six months by suitable fixation and by massage and movements for a further year.

Now the child aged five years shows the right arm held in marked internal rotation and slight forward flexion at shoulder, with about 20° flexion and full pronation at elbow. There is slight wasting over tip of shoulder, and some generalized atrophy of hand with shortening of $\frac{1}{2}$ in. in the arm and less than

½ in. in the forearm. Bony points are normal, but there is definite limitation of passive external rotation (45°), while passive abduction is almost full. The deltoid can fix the shoulder and move the arm slightly only with minimal load. Normally abduction is by the scapula, and the hand can be raised only to level of chin, while active external rotation is deficient. At the elbow there is deficient full passive extension, and about half full supination. Active extension and flexion at the elbow is functionally satisfactory, but the deficient supination and the internal rotation of the arm do not allow the palm of the hand to be turned upwards. There is no actual paralysis of the forearm or

FIG. 2.—Case 5. The effect of disuse.

hand muscles, but with insufficient function there is considerable atrophy of hand with loss of skin creases ; nails and finger pulps normal.

X-RAY : Small cervical ribs both sides.

This patient received fairly adequate treatment and recovery is disappointing owing rather to muscle weakness than to contractures. Muscle involvement is not more extensive than usual, though some pre-fixation of plexus is suggested by cervical ribs.

Case 5. A female infant three months old was brought to hospital with the right arm limp following a difficult birth. When four months old, subscapularis

tenotomy was performed and followed by supervised massage and movements for three months.

Examination at the age of six years shows a normal shoulder outline, no internal rotation of the arm, slight flexion at the elbow, marked wasting over the extensors, right arm shorter than left by $\frac{1}{2}$ in., forearm by $1\frac{1}{4}$ in. (figs. 2 and 3),

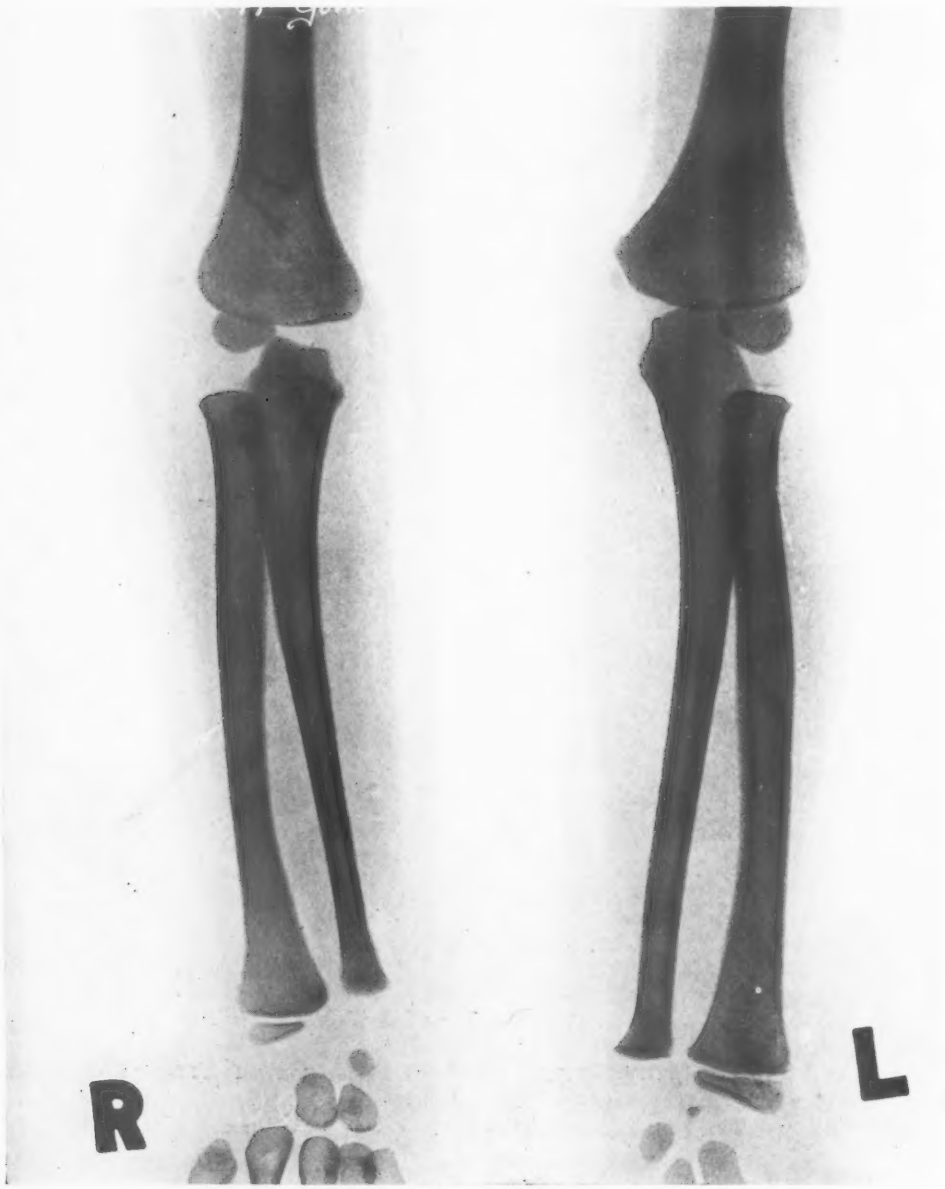

FIG. 3.—Case 5. Atrophy of forearm bones.

slight ulnar carpal deviation and wrist drop in rest position. There is less than 45° limitation of active external rotation at shoulder, and definite limitation of abduction which occurs by scapular movement unless with minimal load. The main residual weakness is in carpal extensors—in grasping dorsi-flexion does

not occur and there is slight abduction weakness of thumb. The hand is poorly developed, but all intrinsic muscles are normal.

This patient shows less disability than usual at shoulder and recovery of external rotation better than true abduction. Persistence of wrist drop is no evidence of whole arm lesion. The better explanation is that the carpal extensors are, at least, sometimes supplied by fifth and sixth (Harris, 1904) or even fifth cervical root (Sherren, 1906).

Case 6. A male, full time and the fourth child of an otherwise normal family, was born after a difficult labour and after internal version for a transverse

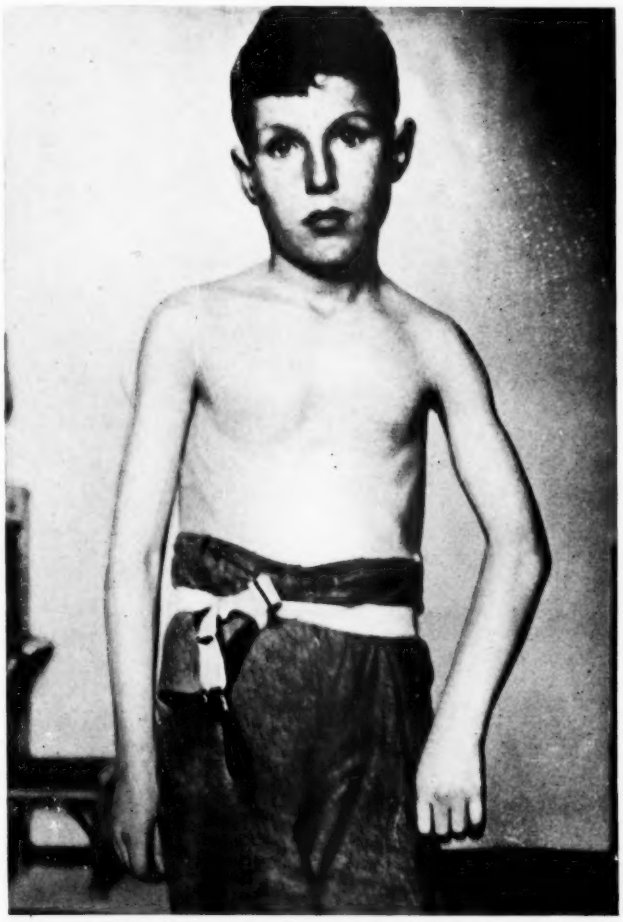

FIG. 4.—Case 6. Marked contractures and subluxation of shoulder joint.

presentation. The left arm was limp, but there were no other birth injuries and no asphyxia. He received no treatment until he first attended hospital at the age of seven years, when an attempt was made to improve position of forearm by excision of the head of the radius.

At the age of ten years he is a healthy, active boy of good nutrition showing definite flattening in front of left shoulder, some wasting of deltoid and spinati, the arm fixed in abduction 30° from the side, in slight forward flexion and gross internal rotation (fig. 4). The humeral head can easily be felt displaced back-

wards. There are gross contractures round the shoulder, visibly of the pectoralis major and latissimus dorsi, while only about 30° passive abduction and less external rotation is possible. Scapular movement is full ; the deltoid just contracts and there is no active external rotation. The forearm is fixed in full pronation, elbow extension is 30° short of full, but elbow flexors and extensors contract well. The fully pronated hand can be brought up to the level of the chin (fig. 5). Relative shortening—arm $\frac{3}{4}$ in., forearm $\frac{1}{2}$ in. There is no sensory loss.

Skiagrams show cone-shaped humeral head, arthritic changes, and elongation of the coracoid process (fig. 6).

FIG. 5.—Case 6. To show the disability of internal rotation of arm and pronation of forearm.

There is practically no scapulo-humeral movement. The condition is worse than a bony ankylosis, as internal rotation is disabling. To this there is added gross pronation. The patient is an energetic boy who persists in using the limb, which shows comparatively little wasting.

Case 7. She is the sister of case 4, born after a difficult instrumental vertex birth, fifth child, full time. She has received no treatment, except massage and

movements for one year when five years old. There has been a gradual slight improvement in function, but none noticed during the past two years.

General examination at the age of ten years is negative, without evidence of spinal cord or sympathetic injury, respiratory system normal. There is marked wasting of right arm and chest (clavicle $\frac{3}{4}$ in., arm 3 in., and forearm $1\frac{1}{2}$ in. relative shortening). The right arm hangs abducted in slight forward flexion, not rotated. The forearm is flexed at the elbow 60° from full extension and fully supinated. The wrist is in dorsi-flexion and slightly deviated radially. The metacarpo-phalangeal and inter-phalangeal joints are flexed (fig. 7). Contractures limit extremes of passive shoulder joint movement and extension to within 45° of full at elbow, and permit only 45° passive pronation at elbow.

FIG. 6.—Case 6. Cone-shaped humeral head, flattened glenoid and elongated coracoid.

The shoulder joint is not flail, but is only sufficiently fixed for about 30° weak abduction by scapula, the muscles acting on which are normal. Movement at the elbow is limited to 45° weak flexion, and at the wrist to flexion and extension without load. Efforts at grasping are weak, as the fingers cannot close into palm of hand. The limb can steady an object, but no weight can be carried, nor can the hand be elevated above the level of the breast. There is an area on the ulnar side of the forearm back and front, from one inch below the elbow to the wrist, over which sensation to light touch and to pin prick are lost equally. The flare response (Lewis, 1927) is badly marked generally, but appears to be present over this area. Though the skin is thin and devoid of fine hairs, especially over the analgesic area, there is no abnormality of the nails or finger-tips such as might be considered a ' trophic ' change.

X-RAY : Shortening and rarefaction of bone, but no deformity of humeral head. Some lengthening of cervical lateral processes of seventh cervical vertebra.

This patient shows whole-arm involvement with slight recovery, chiefly of the upper roots. The paralysis at the shoulder is balanced and there are no contractures. Sensory loss suggests complete lesion of sensory fibres to the

FIG. 7.—Case 7. The limb in a whole arm lesion.

affected area from eighth cervical and first thoracic roots, and the flare response suggests a lesion central to the ganglion.

Case 8. In a railway accident a boy of eleven sustained a compound fracture of the right femur and a fracture of the right humerus, while the left arm appeared painful on movement. He was acutely ill for some time and the left arm, which was radiologically normal, was allowed to lie across the chest, the elbow flexed and pronated.

External rotation or abduction at shoulder or handling the limb, especially pressure over the extensor muscles arising from lateral humeral condyle, produced severe pain and muscle guarding. This was well marked at the end of

one month and there was no active movement at the shoulder. Transient slight sensory loss over middle third of arm (? sensory branch of circumflex) was noticed in the fourth week. The deltoid started to show wasting, as did the external rotators of the shoulder, elbow flexors and extensors, and to a less extent the forearm muscles, chiefly the extensors, but there was no loss of response to faradism.

Treatment was by massage, radiant heat and supervised movements, and from the sixth week gradual improvement with satisfactory recovery of external rotation and flexion of the forearm occurred. Recovery of full extension at elbow (some biceps contracture) and full true shoulder abduction was delayed until the fourth month. Definite wrist drop was absent throughout.

Was this a paralysis or a pseudo-paralysis? At first a reflex fixation following injury was suggested. The muscle hyperaesthesia, the transient sensory loss, the elbow weakness and the more definite muscle wasting suggested some secondary involvement of nerves. The early and good recovery of the external rotators and the weakness of elbow extension suggest involvement of the posterior cord of the plexus, rather than the nerve roots, but the lesion cannot have been complete, as the carpal extensors were not demonstrably involved.

Case 9. Five years ago a three-year-old boy was admitted with apparently minor injuries sustained in a motor accident while playing on the street. The next day he persisted in refusing to use the left arm, which was radiologically normal and gave no evidence of a shoulder dislocation. He improved slowly when treated for six weeks in an abduction splint and later by supervised exercises.

The left arm now hangs normally from the shoulder, the elbow held in 30° of flexion, slight wrist drop and ulnar deviation of wrist present. Measurement shows relative shortening of $\frac{3}{4}$ in. in the arm and $\frac{1}{2}$ in. in the forearm. Muscle wasting is slight and confined to triceps and carpal and digital extensors. Though the left hand is slightly smaller than the right, all intrinsic muscles are well developed and acting. Abduction of the arm begins with scapular movement, but only slight relative weakness of true abduction, while external rotation is normal. Full extension of the inter-phalangeal joints is only obtained by flexion of hand at the wrist, while finger flexion is not associated with the normal fixation of the carpus in dorsi-flexion. The triceps shows slight weakness. There is no sensory loss, and apart from diffuse rarefaction at elbow and hand the bones are radiologically normal.

The absence of residual paralysis in the external rotators, elbow flexors, or supinators, the weakness just demonstrable in the deltoid (circumflex nerve) and more marked in the territory of the musculo-spiral nerve—especially of the more distal muscles, is suggestive of a lesion of the posterior cord or the nerves arising from it. In a lesion to the upper nerve roots weakness of the finger extensors should be associated with much more extensive residual weakness. The lesion is incomplete, there is no sensory loss and all muscles have retained some power.

Case 10. Two weeks before first attendance an older child lifted the patient, then an infant of fifteen months, from the ground by the left arm. There appeared to be no pain after the first day and he was treated as a minor injury at another hospital. Treatment for almost one year in an abduction splint and with massage and movements produced only slight improvement.

Now at the age of seven years he is of poor general nutrition and muscle development, without evidence of spinal cord or sympathetic nerve injury. The left side of the chest is under-developed, the shortened flaccid arm hangs vertically downwards, without rotation, the forearm slightly pronated. Extrinsic scapular muscles are poorly developed without evidence of paralysis. The pectoralis major, the deltoid and spinati show marked wasting (fig. 8). The deltoid just contracts, but cannot fix the flail shoulder joint for abduction by the scapula. Flexion, extension and supination at the elbow are functionally

FIG. 8.—Case 10, showing wasting of the limb and sharp shoulder outline in a whole arm lesion.

useless, but there is weak movement of the flexors and extensors of the wrist and fingers and the intrinsic hand muscles are acting.

Radiologically the limb bones show atrophic changes and decalcification only. There is no sensory loss.

The most likely injury is to the roots of the plexus, with less involvement or with better recovery of the lower roots. The extreme wasting and flaccidity suggest anterior poliomyelitis, of which there is no other evidence, although the history is insufficient to exclude this. The trophic changes are those following disuse.

Etiology

Obstetrical cases.

INCIDENCE. One patient in slightly over every three thousand children attending the out-patient service of the Belfast Hospital for Sick Children suffered from a birth palsy. The incidence thus appears to be much lower than Duval's figure of one in every two thousand births usually quoted (Thornburn, 1903 ; McFadden, 1928). Fleming (1931) reported twenty-eight cases in eight thousand hospital deliveries. The injury appears to be sustained at birth ; there is nothing to suggest a developmental abnormality. The variable factors are thus : (1) The child ; (2) the mother ; and (3) interference from without —the midwife.

THE CHILD. All the cases reviewed have been born by full-time labours, and in many the baby was considered abnormally large. No sex incidence has been observed in any large series. In this series girls were more often affected than boys both in vertex and breech deliveries (seventeen girls to nine boys). An important factor would appear to be the size of the head relative to the shoulders. A large head will, within limits, dilate the passages for the shoulders in a vertex presentation, but will occasion the difficulty in a breech presentation. Of the vertex presentations eight involved the right and seven the left arm, and of eight breech presentations one was bilateral and two involved the left arm. Three transverse lies were dealt with by version late in labour. The high incidence of presentations calling for some interference is significant. In 50 per cent. of cases a definite history of a high degree of cyanotic asphyxia and delay in starting respiration was given. Fairbank (1913) stated that many of his cases were black at birth. This cannot be correlated with the ultimate extent of the lesion. Although cases of phrenic nerve involvement are reported (Kofferath, 1921 ; Epstein, 1927, quoted from Gordon and Forrester Brown, 1933), a special examination of the respiratory system, including screening in two cases, and enquiry as to repeated attacks of pneumonia was negative both in infants with and without asphyxia at birth. A relaxed asphyxiated infant, the product of a difficult labour, is more likely to allow undue separation of hard parts and thus increase the liability of injury of soft parts.

THE MOTHER. The mothers varied from a primigravida of nineteen years to a multipara of forty-one in her eighth pregnancy. The few really long labours were apparently in all cases associated with abnormal presentations. Twelve out of twenty-six cases (46 per cent.) were first labours. As the average family in the series was 4·3, this suggests some association with what is generally the most difficult labour. Although two sisters (cases 4 and 7) sustained obstetrical palsies, there was no apparent familial increase of birth injury of any kind, and the mothers do not represent any class of difficult labour case.

INTERFERENCE FROM WITHOUT. Only one labour can be regarded as normal : all the rest appear to have required some assistance, usually quite early in labour, and all had anaesthesia for a short time at least. In the great majority the application of forceps (thirteen out of fifteen vertex cases), version late in labour (three cases), manipulations to bring down an arm in a breech case (one

case) or great difficulty in delivery of the shoulders (three cases) was described. The association of other injuries in some of these cases, a broken femur in one, bruising of the whole of the affected side, extensive cuts to the face and head (four cases), and probably the increased frequency of sterno-mastoid tumours are suggestive of unusually difficult labours. In Sever's large series of eleven hundred cases only 5 per cent. were normal labours.

POST-NATAL INJURIES. The varied and often uncertain mechanism of traumatism is illustrated by cases 8, 9 and 10. Williamson (1897) and Vandenbossche (1910) emphasize the great variety of the traumatic force, often slight and almost unnoticed at the moment, such as carrying a weight on the shoulder with the head inclined to the opposite side or a slip while carrying a heavy weight in the hand. One infant of eighteen months had a brachial paralysis because his father had suddenly snatched him up by the armpits (compare case 10). Only occasionally is a dislocation of the shoulder associated even in the adult.

Clinical investigation

In general this group of twenty-nine children are of average health and nutrition, and appear to lead a fairly normal physical and mental life. One case (case 6) apparently showed a tendency to over-compensate for his disability by noisy, aggressive behaviour with his companions.

Inspection. The appearance of the affected limb varies with the degree o involvement and with the many complex factors in recovery—muscle balance, contractures, muscle wasting and so-called trophic changes. The typical position in the early cases is well known. The deltoid (cervical nerves, fifth and sixth, i.e. C.N. 5–6 ; or C.N. 5 (Harris, 1904)) and the spinati (C.N. 5–6 or C.N. 5, Harris) are paralysed. The sternal head of the pectoralis major (C.N. 8 and Th. 1 or C.N. 6–7–8 (Harris)) and latissimus dorsi (C.N. 6–7–8) escape in great part and cause the characteristic rotation inwards of the arm. The elbow is extended, the triceps (C.N. 6–7–8) either escaping altogether or being less involved than the flexors (C.N. 5–6). The supinators of the forearm (biceps and supinator brevis and possibly brachio-radialis supplied by C.N. 5–6 or C.N. 5 (Harris)) are paralysed, as is usually the pronator teres (C.N. 6 or C.N. 5 (Harris)), but the pronator quadratus will produce pronation of the fore-arm. This with the marked internal rotation of the arm causes the palm of the hand to look backwards and laterally (see fig. 1). The radial flexors of the wrist (C.N. 6 or C.N. 6–7–8, Harris) may be weakened sufficiently to allow ulnar deviation by the flexor carpi ulnaris (C.N. 8, Th. 1). The persistence of some carpal extensor weakness should not be regarded as evidence of a whole arm lesion (compare cases 5, 7, 9 and 10).

Improvement will occur in almost all cases, usually starting first in the peri-phery, probably as the more distal muscles receive a smaller part of their nerve supply from the upper roots. In a number of patients, in whom muscle imbalance has resulted, either from slow or no recovery of paralysed muscles, contractures and often some degree of subluxation of the head of the humerus

develop, and the limb assumes a different rest position (case 4 and especially case 6). On inspection (fig. 4 and 9) there is slight abduction, usually less than 45°, and marked internal rotation of the humerus. The humerus is slightly flexed forwards (abducted in the antero-posterior plane). The outer part of the scapula may be a little further forward than usual owing to the new position of the limb and probably also to pectoral contracture. The pronated forearm is usually flexed at the elbow, though rarely more than 30°.

Palpation. As Thomas (1916) emphasizes, the humeral head projects

FIG. 9.—Developing contractures less marked than in case 6 (fig. 4).

normally in front of the acromion as much as it does outside it, while there is a depression on pressure of the examining finger under the posterior edge of the acromion. Departure from this, associated in some cases with visible flattening of the front of the shoulder and fullness below the angle of the acromion behind, has been sufficiently marked in six cases to indicate a posterior subluxation. The anterior subluxation described by Bullard (1907) has not been seen. The humeral head probably tends to be driven in whatever direction the muscle support of the joint is most deficient.

In fifteen of the twenty-seven arms involved in birth injuries there was residual limitation of passive external rotation of the arm. This was associated constantly with contractures demonstrable in the pectoralis major and latissimus dorsi, and possibly of the subscapularis tendon, and in over half of these cases, including all the most marked, full extension at the elbow was also limited. Passive abduction at the shoulder joint can be tested in different positions of the arm, ranging from so-called abduction in the antero-posterior plane to abduction in the coronal (frontal) plane. Abduction in the mid-position (McGregor, 1937) or true scapular plane (Johnston, 1937) is the most important. In the coronal plane full elevation is only attained by external rotation of the humerus (Martin, 1932 ; McGregor, 1937 ; Johnston, 1937). Thus contractures tending to fix the arm in internal rotation may act as an additional limiting factor to abduction. Limitation of passive abduction, confined to those patients showing quite definite limitation of external rotation, was always associated with contractures, often marked in the latissimus dorsi and teres major. Contractures of the inferior gleno-humeral ligament (McFadden, 1928) and elongation of the acromion process (Sever, 1920) are probably not primary causes.

Active movements. Although it is easy to determine that a joint moves, it is by no means easy to determine beyond doubt what agent causes its movement. This necessitates a study of the rôle of the different muscles in carrying out movements, and a realization that muscles, as Beevor (1903) has emphasized, have no independent or isolated existence. The nervous mechanisms will use any agent capable of carrying out the motion required. The optimal position for contraction, the elimination of gravity, the limitations of contractures, and the fixation of the proximal parts must also be considered.

In two patients the scapula of the affected side showed ' winging,' and this prominence became more marked as the patient tried to abduct the arm towards the horizontal or pushed with the outstretched limb against a resisting object. In itself prominence of the scapula with the arms by the side is without significance and is usually bilateral. In view of the difficulty of adequate examination in the presence of other paralysis about the shoulder, a difficulty appreciated by Duchenne (1872), it appears likely that the site of injury may in some cases involve the nerve roots proximal to the origin of the long thoracic nerve or that the nerve may be involved in its course behind the plexus by secondary scar tissue. Bullard (1907) almost alone affirms that the serratus magnus is usually involved, but only refers to ' winging ' of the scapula. In all cases failing to show complete recovery, with some residual deltoid weakness or a joint fixed by contractures, the inferior angle of the scapula, if free, began to move outwards from the beginning of abduction. This movement is to be distinguished from the slight gliding motion emphasized by Lockhart (1930) as occasionally marking the beginning of arm abduction, which normally proceeds for almost 45° before the scapula commences to move.

In almost all cases of birth paralysis the loss of the power of true external rotation is more marked than that of true abduction. If the scapula is free this is even more fully emphasized, and it is this, often variably developed, scapular mobility which renders such functional tests as attempting to touch the nose,

eyebrows, the back of the head or the vertebral spines of uncertain significance in examining true shoulder joint movements. The limitation and weakness of supination at the elbow, often imposed by contractures, further increase the functional disability of internal rotation of the arm (fig. 5). Only in the patients with involvement of the whole arm is there any permanent functionally significant weakness of flexion and extension at the elbow.

Owing to ' trick ' movements of the fingers by the long forearm muscles (Wood Jones, 1920), paralysis of the intrinsic hand muscles is difficult to exclude. While there may be general wasting, possibly from disuse, some of the muscles may be seen or felt to contract. In root lesions paralysis confined to these muscles with tendency to develop a claw hand should only occur in lesions of the first thoracic root (Klumpke's paralysis). In whole arm lesions the wider extent of the lesion rarely permits gross imbalance.

Sympathetic lesions. Anatomically pupillary inequality and other evidence of sympathetic involvement should only be encountered in lower or whole arm lesions. Sever (1920) finds it ' in a good many cases ' and not apparently confined to whole arm lesions. It was absent in patients with involvement of the whole arm (cases 7 and 10) and in a patient with early lower arm lesion seen since the rest of the series. Its absence does not at all exclude injury to the lower roots and its presence is inconstant (Vandenbossche, 1910).

Sternomastoid tumours. Sternomastoid tumours occurred in seven cases (27 per cent.), in two involving the opposite side to the affected arm. The association is mentioned in Middleton's paper (1930) on sternomastoid tumours ; he found eleven out of fifty-four case records of Erb's paralysis showed the presence of such tumour.

Trophic changes. Changes in growth and nutrition of the limb have been but little studied and generally dismissed as ' neurotrophic ' (Frauenthal, 1912 ; Sever, 1920). In almost all patients showing residual paresis there is shortening of the limb bones, affecting the arm and forearm. In one case, associated with some weakness of carpal extensors and disuse of the forearm, this was most marked in the forearm (case 5, fig. 2 and 3). In severe cases with a practically useless limb the clavicle shows marked shortening, up to 1 in., on the affected side. The scapula and indeed the chest of the affected side may be under-developed (cases 7 and 10, fig. 7 and 8). In a few cases the unaffected limb may show compensatory hypertrophy. Skiagrams show the bones to be decalcified and thinner than on the normal side with sometimes the later appearance of ossific centres. Over an analgesic area in case 7 the skin was thin, shiny and devoid of hairs ; in this and in the hands of two other cases (case 5) associated with disuse there was a deficient development of the natural skin creases, but the pulp of the fingers and the nails were not abnormal. There is no evidence that the sympathetic exerts any influence on growth or muscle function. All changes seen are such that disuse and diminished blood supply would explain. Few trophic changes can be regarded as due to the withdrawal of the direct nutritional influence of nerve cells on affected cells (Lewis, 1936).

Sensation. In eight cases dependable observations on sensation were possible. In case 7 an equal loss of sensation to pin-prick and light touch

suggests comparison with those cases showing similar type of loss following division of the dorsal roots or the roots of the plexus (Head and Sherren, 1905). The flare response (Lewis, 1927) over this area was positive, suggesting a lesion proximal to the posterior root ganglion. Two upper arm birth palsies showed sensory loss over the lateral aspect of the arm—almost over the deltoid insertion. Sensory loss has been described in the adult traumatic cases (Williamson, 1897), but is stated to be usually transient (Warrington and Jones, 1906). The fifth and possibly the sixth cervical root can be divided without sensory loss (Sherren, 1906).

There was no correlation in the upper arm lesions between residual sensory loss and extent of motor paralysis. Pollock (1934) in a detailed investigation, found no specific relation between the return of sensation in individual nerve fields and motor recovery in muscles deriving their nerve supply from the same mixed nerves. The most marked bony changes were associated with absolutely normal sensation (case 6), and joints radiologically normal with sensory loss while contractures developed in the presence of, or without, sensory loss.

Radiography. Certain changes are described (Sever, 1920, 1925 ; Gilmour, 1925 ; Jepson, 1930 ; McMurray, 1937), which, however, are of no diagnostic value. The humerus may be somewhat atrophic with alteration in trabeculae, the glenoid flattened and with arthritic changes, the coracoid elongated and the acromion show hooking or ' beak ' formation (McMurray, 1937). The most definite change, though seen but twice in well-marked cases of subluxation, is the development of a cone-shaped humeral head, flattened side next the axilla (case 6, fig. 6). Cervical ribs were present in one case (case 4) and the cervical lateral processes of the seventh cervical vertebra were elongated in another (case 7). While x-rays may not always reveal the presence of cervical ribs (Southam and Bythell, 1924) there is no significant demonstrable evidence of a high incidence of prefixation of the brachial plexus. Radiologically there was no evidence of any epiphyseal lesion. In cases showing deficient full extension at the elbow this was not associated with the demonstrable bony changes found by Bullard (1907).

Electrical reactions. Only in one case (case 8) were these employed. A general anaesthetic is required in young children for accurate localization of response (Fairbank, 1913) and the results are often misleading in prognosis (Froelich, 1921). The volitional test scientifically employed will give as much information as the equally difficult electric tests, and greater help with the more important question of the muscle balance of joints.

Pathology

There is considerable operative data (Kennedy, 1903, 1904 ; Taylor, 1921 ; Boorstein, 1923) to support the involvement in upper arm cases of the fifth and sixth roots, or sometimes the fifth alone (Sherren, 1906 ; Fairbank, 1913) proximal to the plexus. At least half the cases showing residual weakness appear to require a more extensive lesion than the avulsion of the supra-clavicular nerve suggested by McFadden (1928). Boyer (1911–12) reports an

autopsy on a long-standing case in which definite changes in the antero-lateral region of the cord were found, and Sever (1925) claims to find cord injury in a ' noticeable number ' of cases. Every case was examined for evidence of residual lesion and questioned for significant delay in learning to walk with an entirely negative result.

Lesions may be produced in the cadaver illustrating that the effect of forcible traction, pulling the head to the opposite side, or rotation of the head is maximal on the upper roots of the plexus, owing chiefly to their more acutely downward course, and that the roots tear before the plexus or the branches (Sever, 1920 ; McFadden, 1928). These can only give information as to a possible mode of production of what is often a severe grade of lesion and make no recognition of the effect of pressure from haemorrhage or scar tissue formation following laceration of the deep cervical fascia. Those patients making a complete recovery (e.g. case 2) show such rapid improvement that in them pressure from blood or oedema of neighbouring parts seems probable. Direct pressure from forceps should only produce the lesion if associated with gross damage to superficial structures. Traumatism from the clavicle is considered by Williamson (1897) and Derganz (1930). Kustner in 1889 and Peltesohn in 1914 (Froelich, 1921) suggested a fracture of the upper extremity of the humerus with secondary involvement of nerves. Shortening is better explained by disuse than by such co-called epiphyseal injury (case 5, fig. 2 and 3).

T. Turner Thomas (1911, 1914, 1916) from a study of shoulder-joint injuries in adults advanced the view that laceration of the axillary portion of the capsule, following sprains and dislocations, and the resultant extravasation of blood, lymph and synovial fluid set up a non-infective inflammation around the branches of the brachial plexus. In obstetric cases he regards the subluxation as primary and resulting from direct pressure by the maternal pelvis. This view is strongly opposed by Taylor (1921). In cases of obstetrical palsy the presence of demonstrable displacements at the shoulder joint only in cases of some duration, the existence of intermediate lesions apparently connecting such subluxation with the slow development of contractures at the shoulder and often also at the elbow has given no support to this view. In cases 8 and 9 ' sprains ' of the shoulder joint must be considered in the etiology of lesions of a somewhat different nature. In the latter there is no involvement of the external rotators : the territory of the muscle paralysis is practically that of the posterior cord. In the former the arm is rendered motionless, painful, resisting passive movement, with paralysis more extensive than severe in any one muscle group, with muscle wasting, transitory slight sensory loss, muscle hyperaesthesia, associated with rapid recovery, in particular of the external rotators, residual weakness being mainly in the elbow extensors. This patient was closely observed over a prolonged period, and at all stages appeared to differ materially from the picture presented by any birth palsy.

Diagnosis

A careful history and some patience in the examination will usually lead to a diagnosis in the birth palsies. In a few cases seen late, and especially in the post-

natal traumatic lesions, the localization of the lesion and even the nature of the lesion may be decided only in terms of probability. A realization of the different picture presented at different stages, a detailed correlation of muscle weakness with possible injury in nerve trunks, nerve roots, or anterior horn cells, with an appreciation of the individual variations, is essential.

The arm may be held motionless and in the typical position from reflex guarding in any painful condition about the shoulder, and for Thomas, Peltesohn and others this pseudo-paralysis is the primary cause of the rest position of the limb. A limp, flaccid limb, usually painless on movement, immediately after birth will almost exclude epiphyseal separation or primary subluxation of the shoulder—if, indeed, these ever occur. Birth fractures, occasionally showing temporary wrist drop later from involvement of the musculo-spiral nerve, may be considered. Syphilitic epiphysitis, the pseudo-paralysis of scurvy, early osteomyelitis or tuberculosis of the shoulder joint in the slightly older child can be excluded. Occasionally children recently lifted by the arm or shoulder are seen who have since ceased to use the arm. Passive movement is usually free and painless ; active movement may appear absent for some hours or even overnight, though often careful examination reveals some power in all the muscle groups (compare case 10).

Of the spastic or cerebral palsies a monoplegia is the rarest. Evidence of hemiplegia or diplegia, mental and developmental arrest and the preservation or return of clumsy, coarse movement at the proximal joints, while the hand movements are more affected will be helpful. Anterior poliomyelitis may cause real difficulty in the lesions of older children, the febrile period and the transient involvement of other muscles escaping the notice of the parent. In cases studied with residual arm involvement the incidence on the deltoid was marked, but external rotation was proportionately less involved. In uncomplicated root lesions the external rotators appear to be the last muscles to recover. The possibility of pressure on the spinal cord or roots by spinal caries, tumours, syringomyelia or cervical rib (lower arm, or Klumpke type of lesion only simulated) may be considered. Behaviour in nerve injuries does not suggest the more constant pain of pressure lesions. Adequate examination will exclude infantile muscular atrophy of spinal origin, the myopathies or functional disease in older children.

Prognosis

Trainor and Crothers (1923) from Sever's clinic consider that full recovery is exceptional. Fleming (1931) obtained recovery in the great majority of his cases (twenty-one out of twenty-eight cases). Though a completely useless arm is rare, there appears to be no guide but the progress of the case. Provided contractures are prevented every patient will improve—often for years. In this group of twenty-six cases involving twenty-seven arms (one bilateral) six made a complete recovery. This recovery was complete or all but complete within three months, a finding supported by Boorstein (1923). In five examples of incomplete recovery function was chiefly limited by weakness of the external rotators, the hand being brought to the mouth or forehead in a useful position,

deltoid action being full or almost full. Six arms showed a varying degree of posterior subluxation with proportionate degree of development of firm contractures and limitation of movement. One virtually untreated patient with whole arm involvement although showing no subluxation has functionally almost a useless limb. In the remaining nine arms, including two still under treatment, contractures have failed to cause definite subluxation, but limit external rotation and abduction so that in only a few can the hand be raised above the level of the chin. In hospital a number of late cases which have failed to improve may be seen. However, all but five patients (six paralysed arms) attended before the age of three months, and, of these, all but two before the age of two months. Omitting late cases there are six complete recoveries in twenty-one cases (29 per cent.), and a good functional result in four (19 per cent.), while only two treated cases show subluxation. Reference to the case notes (cases 8, 9 and 10) will show how difficult and guarded prognosis must be in post-natal traumatic cases.

Treatment

Complete recovery has followed inadequate treatment, and might follow no treatment in many cases recovering within three months. The justification for energetic and painstaking treatment is the relatively better function and freedom from contractures in the thoroughly treated patients. The paralysed muscles must be placed in a position in which they are relaxed beyond their normal position of equilibrium. A splint (Fairbank, 1913 ; Platt, 1921 ; Boorstein, 1923) may be used to hold the arm in right-angled abduction and should maintain it well braced back to prevent pectoral contractures (Mackenzie, 1930), and with the forearm in right-angled flexion and pronation, correcting wrist drop or carpal deviation if present. A collar and cuff fixing the dorsum of the hand to the back of the head has given adequate fixation in eight out of ten early cases in which it was employed. With intelligent co-operation it is especially useful in such cases. McMurray (1937) advises this method in the young infant.

The use of movements, often associated with music, passive at first and later active, has been advocated, splints being used only for developing contractures (Trainor and Crothers, 1923 ; Sever, 1925 ; Gordon and Forrester Brown, 1933). Education of true shoulder muscles is difficult owing to free scapular movement. It seems better that early fixation should prevent contractures. Supervised movements are of great value, but may supplement rather than replace fixation in the practice of most clinics. Electricity appears to have little place in treatment ; indeed Boorstein (1924) describes its use as cruel.

The subluxation may be treated by forcible manipulation on one or more occasions and prolonged fixation in plaster (Whitman, 1905 ; Thomas, 1914, 1916). Platt (1921) and Gilmour (1925) think this only suitable for infants and young children. In the open operation (Fairbank, 1913 ; Sever, 1920, 1925 ; Taylor, 1921 ; Boorstein, 1923 ; McMurray, 1937) the subscapularis and occasionally the pectoralis major tendons are cut to allow full rotation and abduction of the humerus. Some range of movement at the shoulder joint

should be present and the joint free from arthritic change before operation. In two cases the subscapularis tendon was divided before the age of six months. Now five years later in both cases the joint has an almost full range of passive movement, is rather lax, active external rotation is limited and functionally of reduced value owing to weakness, while the true shoulder abductors are acting very little (fig. 10). In another case two operations after the age of six years have failed to prevent internal rotation, owing to the inadequate recovery of

FIG. 10.—Subscapularis tenotomy, but function still limited owing to persistent muscle weakness.

the external rotators, the possible extent of which cannot be predicted before operation. The variety of tendon grafting operations is evidence of their general uselessness. Suggested bone operations include correction of internal rotation by a humeral osteotomy, and ankylosis for a flail shoulder joint, but only if elbow movement is satisfactory. Taylor (1921), who has had a considerable experience of operations directed to the damaged nerves, now prefers to wait as long as any improvement is taking place. In the hands of a few such operations are perhaps justified in patients with whole arm lesions showing no recovery.

The treatment of post-natal traumatic injuries is directed on similar lines to that of birth palsies. A metal abduction splint will be required, and more active co-operation may be hoped for from the patient.

Summary

The progress over a number of years of an unselected group of cases with birth and post-natal brachial nerve palsies has been reviewed and an attempt made to describe and correlate the changes with the possible site of traumatism.

Although the distribution of paralysis in birth palsies supports in general a rupture of the nerve roots from forcible overstretching a variable picture is presented. Two post-natal injuries depart so much from any such picture as to suggest the involvement of the posterior cord or the nerves derived from it, possibly by organization of an exudate from a traumatized shoulder joint.

In the etiology of birth palsies the one almost constant factor is interference from without. Other factors are important as they increase the necessity for this.

Slightly less than one-third of the birth palsies made a complete recovery, and this occurred within the first three months.

Emphasis throughout, especially in treatment, should be on the muscle balance of joints, best determined by a study of voluntary movements, and on the prevention of contractures.

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THE CAUSATIVE ORGANISMS OF BRONCHO-PNEUMONIA IN INFANTS IN EGYPT

BY

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Every paediatrician is familiar with the lack of therapeutic agents in severe bronchopneumonia and the mixed opinions expressed regarding the use of vaccines. The literature of the last fifteen years is full of encouraging results regarding vaccinotherapy in bronchopneumonia, both experimental (Zinssner, 1929 ; Barach, 1928 ; Goodner, 1928) and clinical (Wynn, 1926 ; Hay, 1927 ; Lambert, 1926 ; Forbes and Steinberg, 1931 ; Cardère, 1930 ; Fort, 1927 ; Weill and Dufourt, 1924). However, experience, personal or gained from a careful perusal of the literature, has shown the uncertainty of the results obtained from vaccinotherapy. One of the explanations of these uncertain results obtained by this method of treatment might be that in the preparation of the stock vaccines, no account is taken of the variation in the nature and combination of organisms responsible for the seasonal epidemics from year to year and from country to country. A preliminary step, therefore, before a considered judgement can be passed as to the value of vaccinotherapy in bronchopneumonia in children, would be to identify the organisms responsible for seasonal epidemics in each country and to make the stock vaccines in accordance with the results. It is with this object that an attempt has been made to identify the causative organisms of bronchopneumonia in infants in Egypt.

Methods available

The material for culture was obtained by means of lung punctures during life. Eyre (1910) was the first who tried to examine bacteriologically ' lung juice ' derived by means of an aspirating needle from the affected lobules. He reported on 164 cases spread over a period of seven years extending from January, 1902, to June, 1909. In some of the cases the lung puncture was made during life, but in the majority it was made after removal of the lungs from the cadaver. Culture specimen taken by lung puncture during life is, however, far superior to culture from the focus at post-mortem examination. This last has been practised by Netter (1892), Mosny (1892), Darier (1909) and Glen Liston (1929), but in this method there is no chance of examining the

cases that survive. Also it is well known that, during the agony of death and immediately after, organisms of the upper passages, bronchi and even of the intestine can invade the lung tissue and appear in the culture although they were not the real cause of bronchopneumonia. Dufourt (1927) has cultured lung juice taken aseptically from the cadaver of children who died without any lung affection and has succeeded in isolating staphylococci and sometimes enterococci and B. coli.

Examination of the sputum is of great help if the search is principally for the tubercle bacillus. But it is unreliable for the organisms that can cause bronchopneumonia, as most of them are normal inhabitants of the upper respiratory passages. Moreover, children before the seventh year of life usually do not spit ; they swallow their sputum.

The culture of a swab from the pharynx is also unreliable, because in the pharynx organisms coughed out from the lungs are mixed with those descending from the upper respiratory passages towards the lungs. Therefore, in pharyngeal specimens, it is impossible to be certain if the organisms grown in the culture are the real cause of the bronchopneumonia present.

It seems, therefore, that examination of lung juice taken by lung puncture, during life is the only reliable method for identifying the causative organisms. The culture may prove to be sterile in spite of the presence of bronchopneumonia. Such sterile results have been found in 25 per cent. of Dufourt's cases (1927) and in 90 per cent. of Peyre's cases (1934). We think that this last figure is too high. Probably some difficulty was encountered in hitting the focus.

Technique of lung puncture

Patients were examined clinically and areas on the chest wall where the underlying bronchopneumonia gave most marked physical signs were noted. Skiagrams were taken to confirm the diagnosis and localize the position of the focus. The site of the puncture was chosen according to the clinical and x-ray findings considered together.

Topographically the lungs are divided into upper, middle and lower zones ; and the chest wall is divided anatomically into anterior, lateral and posterior surfaces. Cases that showed, for example, middle-zone opacity were punctured in the same zone either through the anterior, lateral or the posterior surface according to the clinical findings. This method of localization is easy and practical, although it sometimes fails. Occasionally, localizing physical signs were absent while the x-ray showed a definite lesion. In some other cases the clinical zonal localization differed from the radiological picture. The presence of the localizing signs over the upper zone of the lung while the skiagram showed middle or even lower zone opacity was common. In such contradiction of findings the x-ray results were always followed.

Operation

INSTRUMENTS.—

1–2 c.c. all-glass syringe.

2–3 cm. long, soft, ' non-breakable ' hypodermic needle with medium-sized bore and long bevel. The long-bevelled is preferable to the short-

bevelled needle as it aspirates from a larger area of lung when in position.

The syringes and needles should be thoroughly close-fitting and it is advisable to sterilize them when connected.

Ordinary surgical antiseptic measures should be followed with the following precautions :

Sterilize the skin with alcohol.

Rinse the syringe and needle with sterile saline before use.

No local anaesthetic is needed.

POSITION OF THE CHILD.—Either prone or supine with hands over head to clear the axillary area and abduct the scapula. If the child is restless and strong it is advisable to ask the help of two nurses instead of one.

PUNCTURE PROPER.—After the site has been determined the skin over it is sterilized and then fixed in position by the left hand. The syringe is held in

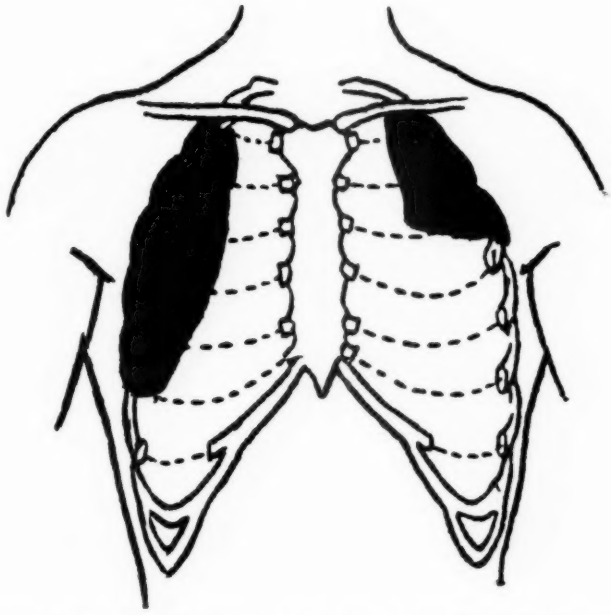

FIG. 1.—Anterior surface of the chest. Dark area is practically safe for lung puncture.

the right hand and the needle is pushed through the chest wall to the advisable depth. The piston is now withdrawn and if nothing comes out, the needle is drawn out of the chest while there is a negative pressure inside the syringe. The advantage of the combined withdrawal of the piston and needle is to prevent infection of the pleural cavity and to have the chance of aspirating the focus in case the point of the needle has been pushed beyond the focus.

FAILURE OF THE PUNCTURE MAY BE DUE TO.—

Failure to hit the focus.

Aspirating blood from sources other than the focus, i.e. liver, spleen and veins.

DANGERS OF THE PUNCTURE ARE.—

Haemoptysis. In two cases a severe paroxysm of cough was noted after the operation. In both the contents of the syringes were mixed with blood. In one of them, a five-year-old child, the sputum was tinged.

The second, an infant of about two years, vomited after the cough and the vomit was tinged. Both recovered.

Infection of the pleura. This can be avoided as explained above.

Hitting heart or great vessels. This can be easily avoided, as will be explained later.

Shock from pricking the pleura. This did not occur in a single case.

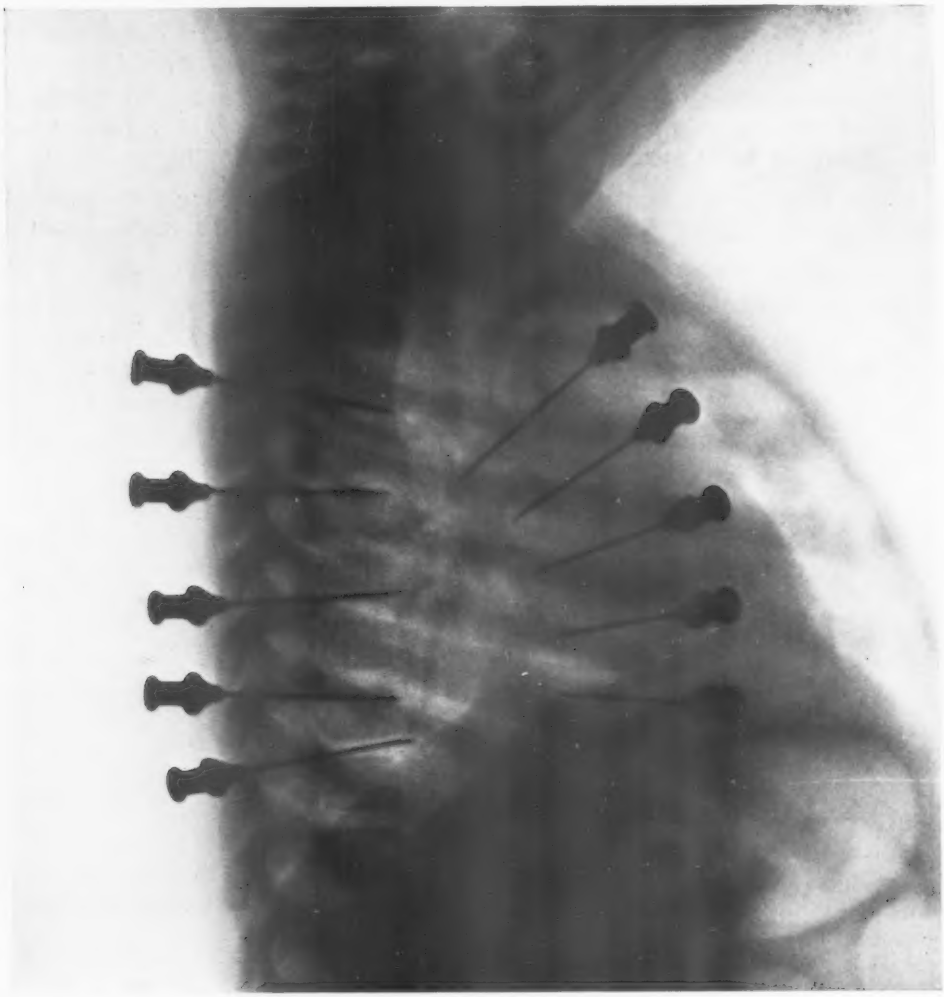

FIG. 2.—Right lateral view of a cadaver with ten needles 3 cm. long introduced perpendicularly to chest wall (on right side) at the anterior and posterior boundaries of the so-called safety zone.

DANGEROUS ZONES.—In order to avoid hitting the heart, great vessels, liver or vertebral column care must be exercised not to introduce the needle in what can be called the dangerous zones. Anteriorly on the right side this dangerous zone lies medial to a line that joins the first intercostal space in the mid-clavicular line with the fifth space in the anterior axillary line. On the left side this line begins as on the right side and descends to the second intercostal space in the mid-clavicular line, then to the third space in the mid-axillary line and ends in the fifth space in the mid-axillary line (see fig. 1, 2 and 3).

Posteriorly the dangerous zone would be medial to a line that starts on either side, above at the fourth space just inner to the medial border of the abducted scapula then drops almost vertically downwards to the eighth space. Above the level of the fourth space the abducted scapula will be in the way. Below the level of the eighth space little lung tissue is left. Between these two lines, above, any enlarged hilar glands at the root of the lung may be punctured ; lower down, medial punctures are not advisable as any unexpected lateral move-

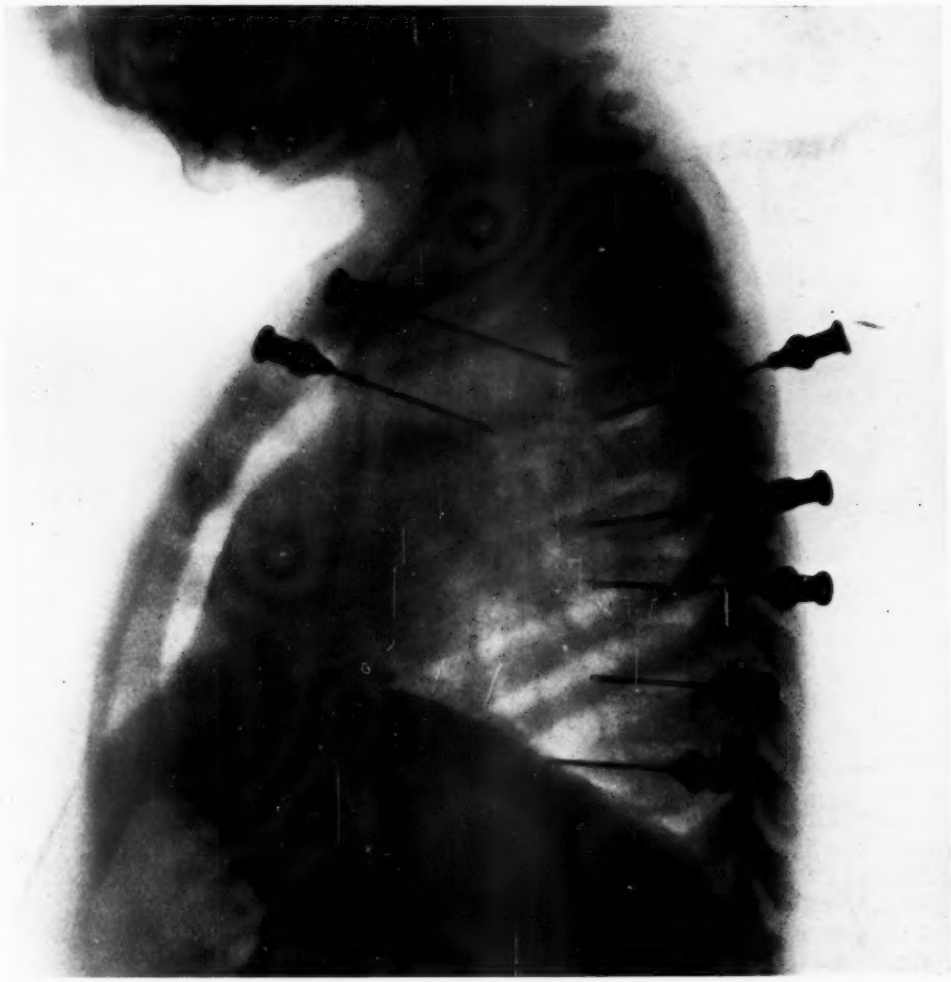

FIG. 3.—Left lateral view of same cadaver as fig. 2 with seven needles 3 cm. long introduced perpendicularly to chest wall—on left side—at the anterior and posterior boundaries of the so-called safety zone.

ment of the child—and this cannot be easily prevented—might cause the needle to hit against the bodies of the vertebrae (see fig. 2, 3 and 4).

If the lesion was detected only by x-ray examination with no physical signs, which shows that the lesion is deep in the lung, the needle must be introduced in the mid-axillary line, perpendicular to the surface of the chest, in the intercostal space level with the lesion. This will point towards the hilum of the lung where bronchopneumonia usually starts.

A needle 3 cm. long when introduced in the mid-axillary line perpendicular

to the chest wall in an infant six months old will be quite far from the heart and great vessels ; and the point will be near to the hilum of the lung. On the right side any of the upper five intercostal spaces can be chosen, while on the left only the upper three are safe (see fig. 5). In younger infants it is safer to use shorter needles, i.e. 2 cm.

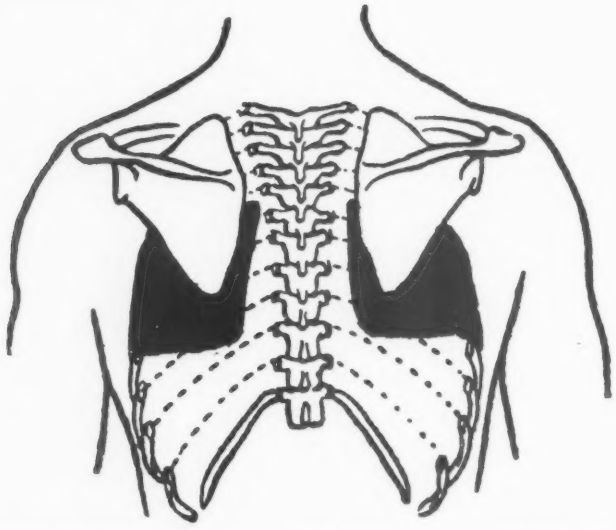

FIG. 4.—Posterior surface of the chest. Dark area is practically safe for lung puncture.

Previous investigations

Other authors proved the safety of lung puncture beyond doubt. C. Robertson Lavalle (1937) in his paper on the treatment of tuberculosis by needle puncture of the lung wrote :

The absolute harmlessness of a puncture performed in the lung has been proved time and again. As long ago as 1917 Dr. Duval presented to the Société de Chirurgie de Paris the results of his first 100 cases of bullet extraction from the lung. With a Kocher's forceps he extracted from the depths of lung tissue, which has already formed a cicatricial mass around the foreign body, bullets as deep as 4–5 inches in the pulmonary parenchyma, and with no after-effects, seeing that the soldiers were discharged after a couple of days. Further, innumerable cases have been recorded bearing witness to Duval's statement at that time : 'The pulmonary parenchyma tolerates the forceps extremely well. Puncture in the lung is just the same as puncturing the gluteal region, the leg, or the arm. Its haemorrhages are insignificant, being either small or limited.'

Results

During the winters 1933–1936, 233 cases of bronchopneumonia were examined clinically and radiologically. These were then lung punctured and the material obtained was stained and examined microscopically and cultured on blood-agar plates and in glucose broth, and these media were then examined for organisms after twenty-four, forty-eight and seventy-two hours' incubation at 37° C.

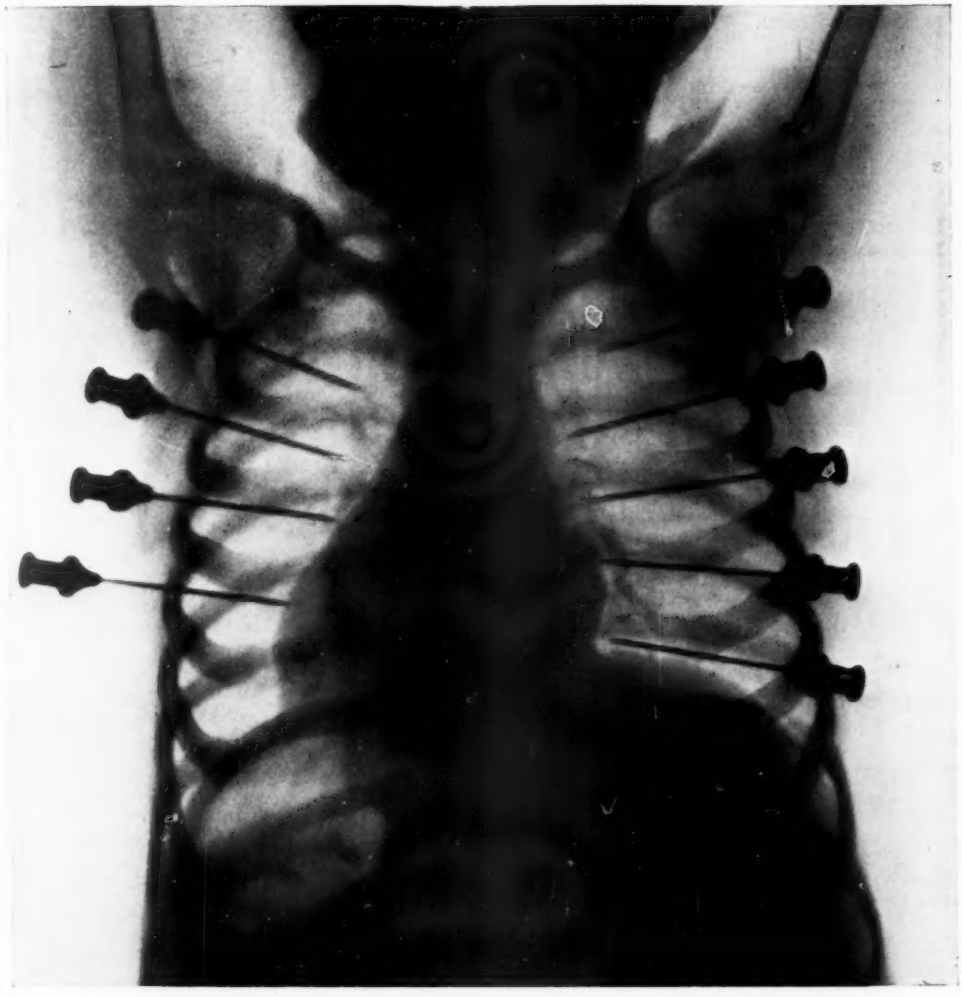

FIG. 5.—Anteroposterior skiagram of the chest of a cadaver with nine needles 3 cm. long introduced perpendicularly to chest wall in the mid-axillary lines right 1–5 and left 1–4 spaces. On right side any of the upper five spaces is safe while on the left only the upper three. The fourth is dangerous.

The following are the results.—

	ALONE	WITH OTHER ORGANISMS	TOTAL
PNEUMOCOCCI	19	13	32
STREPTOCOCCI	20	22	42
B. INFLUENZAE	31	46	77
STAPHYLOCOCCI	21	46	67
B. BORDET GENGOU	4	2	6
M. TETRAGENUS	1	3	4
M. CATARRHALIS	5	25	30
B. PYOCYANEUS	1	0	1
B. FRIEDLANDER	4	7	11
DIPHTHEROIDS	0	8	8

Of the 233 cases examined 51, i.e. 21 per cent., gave no growth on the above media. This probably has been due to difficulty in hitting the focus.

The following table shows the cases caused by more than one kind of organisms and the nature of their combination :

	A	B	C	D	E	F	G	H	I	J
A Pneumococci	**19**	—	5	2	—	1	1	—	1	—
B Streptococci	—	**20**	5	5	—	—	3	—	—	1
C B. Influenzae	5	5	**31**	17	—	—	5	—	1	—
D Staphylococci	2	5	17	**21**	1	—	4	—	3	1
E Bordet Gengou	—	—	—	1	**4**	—	—	—	—	1
F M. Tetragenus	1	—	—	—	—	**1**	1	—	—	—
G M. Catarrhalis	1	3	5	4	—	1	**5**	—	—	—
H B. Pyocyaneus	—	—	—	—	—	—	—	**1**	—	—
I B. Friedlander	1	—	1	3	—	—	—	—	**4**	—
J Diphtheroids	—	1	—	1	1	—	—	—	—	**0**

The following shows the cases caused by three organisms :

No. of cases	
1	Pneum., Strept. and M. Catarrhalis.
1	Pneum., B. Influenzae and Diphtheroids.
1	Strept. non-haem., B. Influenzae and Staph. Albus.
1	Strept. haem., B. Influenzae, and Staph. Albus.
1	Strept. haem., B. Influenzae and M. Catarrhalis.
2	Strept. haem., Staph. Albus and Diphtheroids.
1	Strept. viridans, B. Influenzae and Diphtheroids.
4	B. Influenzae, Staph. Aureus and M. Catarrhalis.
1	B. Influenzae, Staph. Albus and M. Catarrhalis.
1	B. Influenzae, Staph. Albus and B. Friedlander.
1	M. Catarrhalis, B. Friedlander and Diphtheroids.
15 (Total)	

The following shows cases caused by four organisms :

No. of cases	
1	Pneum., B. Influenzae, Staph. Albus and M. Catarrhalis.
1	Strept. haem., Staph. Aureus, M. Catarrhalis and M. Tetragenus.
1	B. Influenzae, Staph. Aureus, Staph. Albus and M. Catarrhalis.

The following table shows the variability of the rate of incidence in percentage of the causative organisms in the different winters :

	1932		1934		1935		TOTAL	
	ALONE	ALONE AND WITH OTHERS	ALONE	ALONE AND WITH OTHERS	ALONE	ALONE AND WITH OTHERS	ALONE	ALONE AND WITH OTHERS
Pneumococci	16·7	27·1	12·3	17·8	3·3	9·8	10·4	17·6
Streptococci	25·0	41·7	10·9	27·4	—	3·2	11·0	23·1
Haemolytic	10·4	18·8	4·1	15·1	—	1·6	4·4	11·5
Non-haemolytic	14·6	22·9	4·1	5·5	—	1·6	5·5	8·8
Viridans	—	—	2·7	6·8	—	—	1·1	2·7
B. Influenzae	10·4	18·8	13·7	42·5	26·2	60·7	17·0	42·3
Staphylococci	4·1	25·0	15·1	35·6	11·5	47·5	11·0	36·8
B. Bordet Gengou	8·3	10·4	—	1·4	—	—	2·2	3·3
M. Tetragenus	—	2·1	1·4	1·4	—	3·3	0·6	2·2
M. Catarrhalis	—	4·2	2·7	15·1	4·9	26·2	2·7	16·5
B. Pyocyaneus	—	—	1·4	1·4	—	—	0·6	1·5
B. Friedlander	—	4·2	—	1·4	6·6	13·1	2·2	6·0
Diphtheroids	—	2·1	—	9·6	—	—	—	4·4

Comment

The above tables show that the pneumococcus (17·6 per cent.) is not the commonest cause of bronchopneumonia in infants. It comes the fourth in frequency after B. influenzae (42·3 per cent.), staphylococcus (36·8 per cent.) and streptococcus (23·1 per cent.). This is quite different from the statistics of other authors. Of the pneumococcal cultures, twenty-seven were typed and the following was the result :

Type I	..	..	..	..	..	4	cases,	i.e.	14·8	per cent.
Type II	..	..	..	..	..	7	,,	,,	26·0	,,
Type III	..	..	..	..	..	3	,,	,,	11·1	,,
Type IV	..	..	..	..	..	13	,,	,,	48·1	,,

Pisek and Pease (1916), Mitchell (1917), Opie (1921) and Thompson, Jr. (1936), gave the following percentages for the different types of pneumococci solated from cases of bronchopneumonia.

	PRESENT RESULTS	PISEK	MITCHELL	OPIE	THOMPSON
Type I	14·8	22·9	11·1	7·6	32·1
Type II	26·0	29·3	11·1	21·9	—
Type III..	11·1	8·3	3·3	5·7	10·7
Type IV	48·1	39·8	74·4	64·8	57·2

The streptococcus comes third in frequency in the present series. Most authors found it second in frequency in their investigations. B. Influenzae is the commonest organism isolated in the present cases (42·3 per cent.). It has been isolated in pure culture in thirty-one cases of seventy-seven when it has been found. This does not agree with Dufourt's findings (1927). He found it almost always associated with other organisms and found it in pure culture only in one case. The staphylococcus has been met with in 36·8 per cent. of the series. It seems to play a definite pathogenic part in the causation of bronchopneumonia. Dufourt has never been able to isolate it by lung puncture in his cases. He denies its pathogenicity in bronchopneumonia, although he has cultured it from the rhinopharynx and at post-mortem examination from the pus of purulent pleurisy secondary to bronchopneumonia. McGregor (1936) and Smith (1935) came to similar conclusions. They consider that the staphylococcus could produce bronchopneumonia either alone or with other organisms. The B. Bordet Gengou, M. tetragenus, B. pyocyaneus and B. Friedlander were rarely met with. The enterococcus has not been encountered in the cultures. This organism has been present in 25 per cent. of Dufourt's cases. The M. catarrhalis, which is said by Duchun (1926) to play a secondary role in the causation of bronchopneumonia, has been met with in 16·5 per cent. of cases and it is concluded that it plays a definite part in the causation of bronchopneumonia. Diphtheroids were cultured from a small number of our cases.

Summary

(1) Lung puncture has been shown to be the best way to isolate the causative organism in bronchopneumonia in early life.

(2) The technique of lung puncture is described in detail and its safety proved.

(3) During the winters of 1932–1936, 233 cases of bronchopneumonia were lung punctured and the material obtained was cultured on blood agar and broth.

(4) Of the 182 positive cases, 106 (58·3 per cent.) showed one organism, fifty-eight (31·9 per cent.) showed two organisms, fifteen (8·2 per cent.) showed three organisms and three (1·6 per cent.) showed four organisms.

(5) The commonest organism found was B. influenzae (42·3 per cent.) ; then staphylococci (36·8 per cent.), streptococci (23·1 per cent.), pneumococci (17·6 per cent.), M. catarrhalis (16·5 per cent.).

(6) Of the twenty-seven pneumococci typed : four cases (14·8 per cent.) were type I, seven cases (26 per cent.) type II, three cases (11·1 per cent.) type III and thirteen cases (48·1 per cent.) were type IV.

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CHINESE METHODS OF INFANT FEEDING AND NURSING

BY

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In any attempt to improve the dietary of a community, it is preferable to evolve from existing practices rather than indiscriminately to substitute foreign ones. It is obvious, then, that these indigenous practices must be known and preferably understood. Mere descriptions alone are often of interest, but their interest and value are enhanced when, as frequently is the case, domestic economies are found on examination to have a sound basis in terms of present-day scientific knowledge.

In relation to infant-feeding problems in China, a general account has been given (Platt, 1936) ; in an appendix to this account, it was indicated that the study was being developed along three main lines : (*a*) a survey of native methods ; (*b*) a critical examination of these in the ward with the aid of laboratory methods ; and (*c*) the translation of the laboratory findings into practice in a typical community. The present paper is a contribution to the first part of this investigation.

The scope of the enquiries is given in the appendix referred to above. The method of enquiry was to take histories from mothers who were attending infant welfare clinics in a native part of Greater Shanghai—for the most part a poor district. The population was drawn from all parts of China, and most of the inhabitants had been in contact with their native place sufficiently recently to retain the habits characteristic of that place. The relationship of the investigators was such that there was no reason to doubt the authenticity of the data presented.

For a sample of 387 subjects, the distribution according to their native province is given in the following table :

TABLE I

PROVINCE	NUMBER OF SUBJECTS
KIANGSU	200
CHEKIANG	111
KWANTUNG	17
HUPEH	17
ANHWEI	9
KIANGSI	6
HOPEH	6
SHANSI	6
SHANTUNG	5
SHENSI	3
SZECHUAN	3
FUKIEN	3
YUNNAN	1

Almost all the subjects were drawn from areas in which rice is the staple article of diet.

It was possible to ascertain the economic status of 187 subjects, and a classification was made into ' good,' ' fair ' and ' poor ' according to the criteria shown in the following table :

TABLE 2

STATUS	BASIS OF ASSESSMENT : INCOME LEVEL—IN SHANGHAI DOLLARS PER MONTH	PERCENTAGE OF SAMPLE
Good	Above 40	26·2
Fair	20–40	20·3
Poor	20 and below	53·5

At the time of investigation, 1 Shanghai dollar = 1*s.* 6*d.*

Breast feeding by the mother was met with in 379 instances in a total of 422 case histories. Of a group of thirty-six in which wet nurses were employed, twenty-six relied solely on milk from the wet nurse. In six cases imported milk powder was employed, and it was claimed by one mother that an infant had been brought up without the use of milk, rice starch powder being the basis of the feeding.

Usual procedure

A picture of the procedure in infant feeding by breast milk in China is afforded by the following description, which is based on the majority of the evidence examined in the investigation. Immediately after the baby is born and again a few hours later, a solution is given which contains some cathartic substance of native manufacture. This is intended to drive out of the body all of the ' heating ' substances. Breast feeding is begun on the second day. A thin paste of rice flour or of starch cake (if the family can afford it), slightly sweetened, is given once or twice daily. In a few days' time, if the supply of milk is adequate, it is found that the child may refuse to take any additional food ; but commonly small amounts of rice flour continue to be fed. Breast feeding when established is irregular, the frequency being determined by the baby's cry. The infant is fed less frequently during the night, and some eight to ten feeds are usually given in the course of twenty-four hours. There is no accepted time for the duration of a feed, which is usually continued until the baby falls asleep.

When the infant attains the age of about five months, soft rice * is introduced into the diet—if the infant can be induced to take it. The amount given varies from two or three ounces twice daily ; sufficient sugar being added to give a slightly sweet taste. After six months of age, some vegetable soup is mixed with the soft rice, which is gradually increased in amount until about

* A brief note of the various preparations of rice is given on p. 348.

three-quarters of the ordinary rice bowl is being taken, at each of two meals, daily.

When the baby is about eight months old, additions are made from the adult diet in the form of a little boiled rice mixed with vegetable soup. At a year, regular feedings of soft and boiled rice are instituted together with soups of various kinds (vegetable, meat or fish), egg, biscuit and oranges. In many places Chinese red ' dates ' (Chinese jujubes) have been fed to babies with the belief, according to Chinese medical teaching, that they promote the circulation and increase the volume of the blood. The ' dates ' (about a dozen for one meal) are cooked and mashed, or an extract is made from them. Whilst they may be eaten at any age, they are usually considered to be primarily a constituent of a weaning diet. By the time the infant has completed his first year of life, he is usually considered to be almost weaned ; but, as will be shown, the child may continue to have breast feeds for many more months.

The importance of good feeding of the mother and wet nurse for successful lactation is thoroughly appreciated by the Chinese. There are recognized rules as to the special food requirements, and the mother is expected to consume a definite number of eggs, chickens, quantities of fish, soup and so forth shortly after delivery. Even with the very poor, every effort is made to fulfil the requirements of tradition. Emphasis is laid on a sufficient supply of fluid, and when milk secretion is poor, drinks of many kinds are prescribed.

There are a number of preparations which are considered to have special virtues as lactagogues. Mashed lean pork is considered to be good ; and a mixture of pork fat and red gram beans (Phaseolus mungo, L. var. subtrilobata, Fr. et Sav.) is sometimes used. Cuttle-fish (Sepia esculenta, Hoyle) is used in the form of a soup alone or together with chicken. Shrimps cooked with red Chinese wine or shrimps' heads in wine are recommended. The use of cooked sea-slugs (Stichopus japonicus, Selenka) has been noted. Rice wine is often associated with supposed galactagogues ; it is taken together with wheat cakes and millet. Special sweet wine made from glutinous rice is sometimes given together with the larvae of blow-fly collected from faeces. A powder made from dead silkworms is made up into a mixture with old wine. The silkworms are those which have not proceeded to the cocoon stage ; their bodies have not decayed, and they are collected as stiff white worms. Noodles (vermicelli) made of wheat with the addition of egg or chicken are commonly taken. Another preparation that is sometimes used is the ' milk ' prepared from the soya bean with powdered walnut added.

Wet nursing

The importance of wet nursing is apparent, and in big cities especially there is a definite system in practice. The wet nurse usually comes in from country areas about two months after she has had her own baby. She may delay for six or seven months if her milk is abundant. Her own infant may be deposited at a foundling home, or she may arrange for a fellow-countrywoman to feed it along with her own baby for a sum of two or three dollars each month. She

attaches herself to a shop in the city which is run as a general servants' agency. The proprietor supplies a baby in order to maintain the milk secretion. The wet nurse pays for room and board provided by the agent, and, if she succeeds in obtaining employment, she pays a fee of half her first month's wages to the agent, and the customer pays an amount to the agent of 80 per cent. of the wages. The employer is expected to pay two months' wages in advance to the wet nurse when she is engaged, and he agrees to pay a bonus of an extra month's wages after the child is weaned. She is expected to serve a probationary period of three days to a week in the home. After her wet nursing duties are completed in the one family, she may be taken on as a servant, she may seek further employment as a wet nurse, or she may return to her own home. It is considered desirable that the wet nurse should have certain qualities. She should be young, healthy, of pleasant disposition, and if possible of pleasing appearance. A primiparous woman is preferred. Her breast development should be ample, and attention is paid to the areola of the nipples, which should be black as an indication of the recent delivery of the nurse's own infant. It is recognized that the milk must be white and thick ; yellow milk, and bluish, thin milk is not good. A test employed is to drop milk on to the table ; the drop formed must be round and raised, and it should not be possible to blow it into smaller drops. A recognized method of determining the quality of milk is by weighing a sample on a special scale which is used for weighing gold ; one pan when full should weigh two ' chien ' and eight ' li.' Another consideration recognized in the choice of a wet nurse is the behaviour of the baby, which should not cry if the milk is satisfactory.

Mixed feeding

If the infant's food requirements cannot be wholly met by human breast milk, the commonest method is to add rice flour or starch cake paste at feeds two or three times in the day. The amounts given approximately during the first two weeks are about 1 oz. each day ; this is doubled in the second month, and in the third as much as 4 oz. a day are given. According to the demands of the child the amounts are gradually increased until a maximum of one bowl of rice mixture (the consistency of paste, one bowl containing 240 c.c.) is given two or three times a day.

Three hundred and ninety case histories have been examined for foodstuffs which were taken in addition to breast milk in what can conveniently be called ' mixed feeding.' The foodstuffs and the frequency with which they occurred are shown in chart I.

The ages at which this mixed feeding commenced for these subjects are given in chart II.

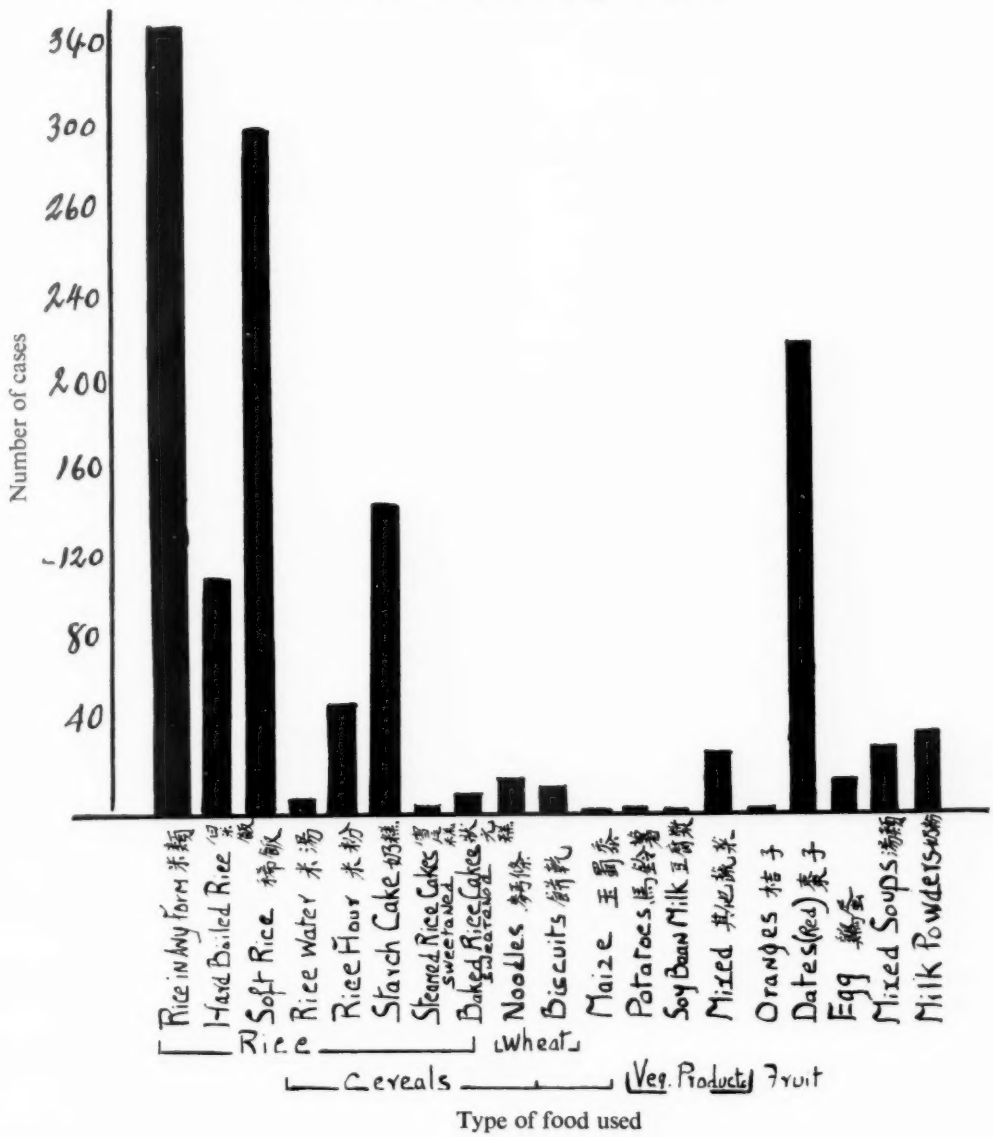
In some of these cases (158) it was possible to get a sufficiently precise statement to be able to say that the foodstuffs had been given because of the insufficiency of the breast milk. If by ' complementary feeding ' it is implied that additional food is being given at the end of each feed on account of insufficient milk, then these cases can be considered as being examples of true

complementary feeding. The kinds of food used and the numbers of instances for each food are given in the accompanying chart (chart III).

The ages at which complementary feeding was introduced were ascertained for 152 infants, and the results are represented in chart IV.

CHART I

The distribution of mixed feeding in 390 cases



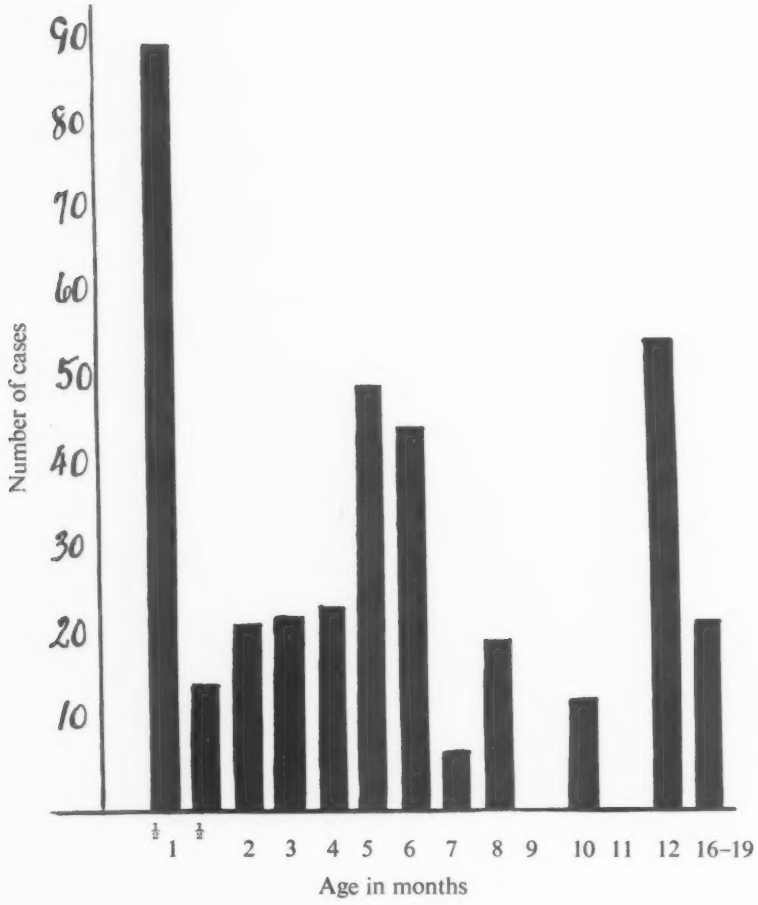
In nearly half the cases complementary feeding was initiated in the first month, especially during the first few days of life. This incidence appears to be accounted for by the practice of starting some additional feeding at birth, as described above, then deciding after a few days that the extra feeding must continue on account of inadequate supplies of breast milk. It is noteworthy

that starch cake was more commonly used in purely complementary feeding. Red 'dates,' it will be noticed, are not given as they appear to be considered peculiar to the weaning diet.

Some of the foodstuffs appearing in the foregoing charts may be described briefly. Soft rice (congee) is made of polished white rice simmered for one hour with six parts of water ; thus 125 gm. of rice with 725 c.c. of water will ultimately yield about two bowls of soft rice. The fluid separated off from the grain in this preparation is known as ' rice-water.' For the preparation of

CHART II

The distribution of ages at which mixed feeding began



' rice-flour,' white, non-glutinous, polished rice is washed and ground in a Chinese stone handmill. The powder is dried, and can be kept for use. It is cooked by steaming with water and a little sugar in the rice-boiler of the native cooking-stove. For infant feeding, either so called ' early seasoned rice ' or ' red rice,' i.e. unmilled rice having a pigmented pericarp, is preferred by some. ' Yellow rice,' a milled rice which has been stored for some months under moderate heat, is not considered good because it is ' rough ' to swallow. Steamed rice cakes (sweetened) are made from finely sieved, polished, white rice flour steamed with additional sugar and then cut up into small pieces.

CHART III

The distribution of 'additional' foodstuffs in 158 cases

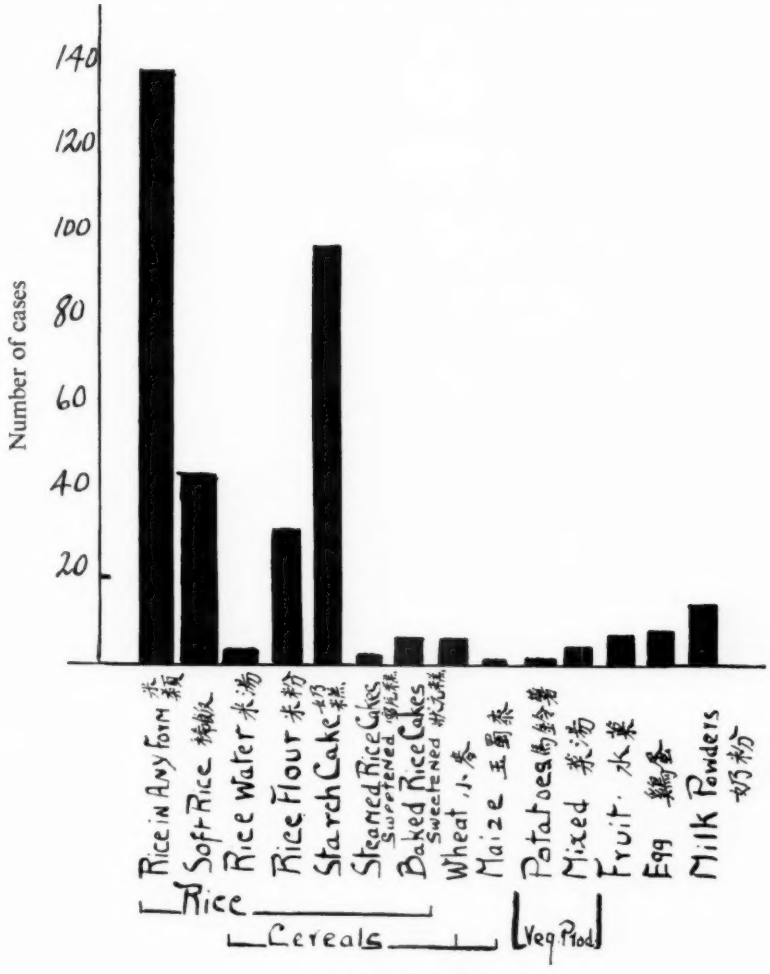
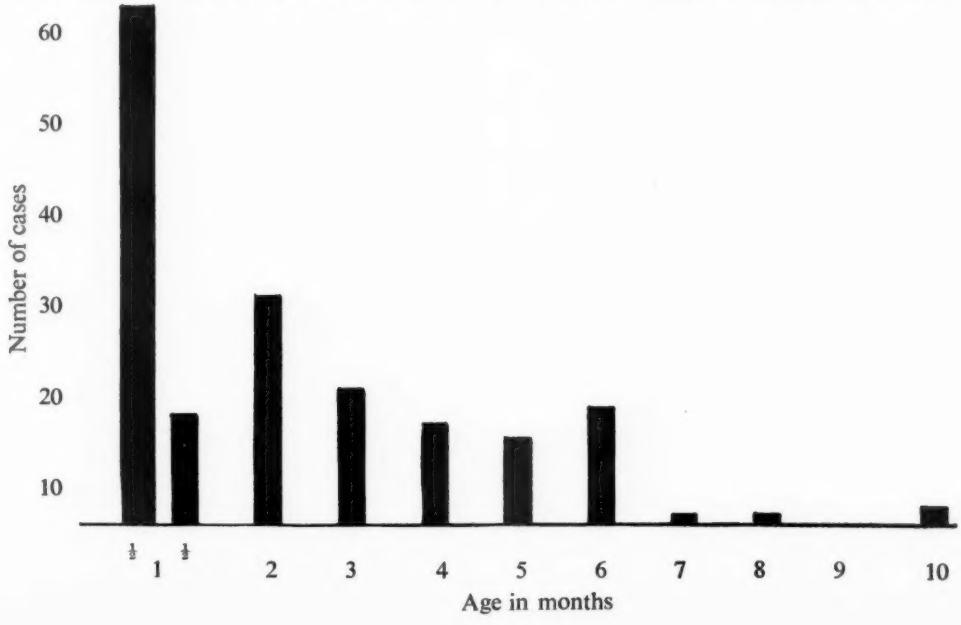


CHART IV

The distribution of ages at which rice was introduced as an 'additional' foodstuff in 152 cases

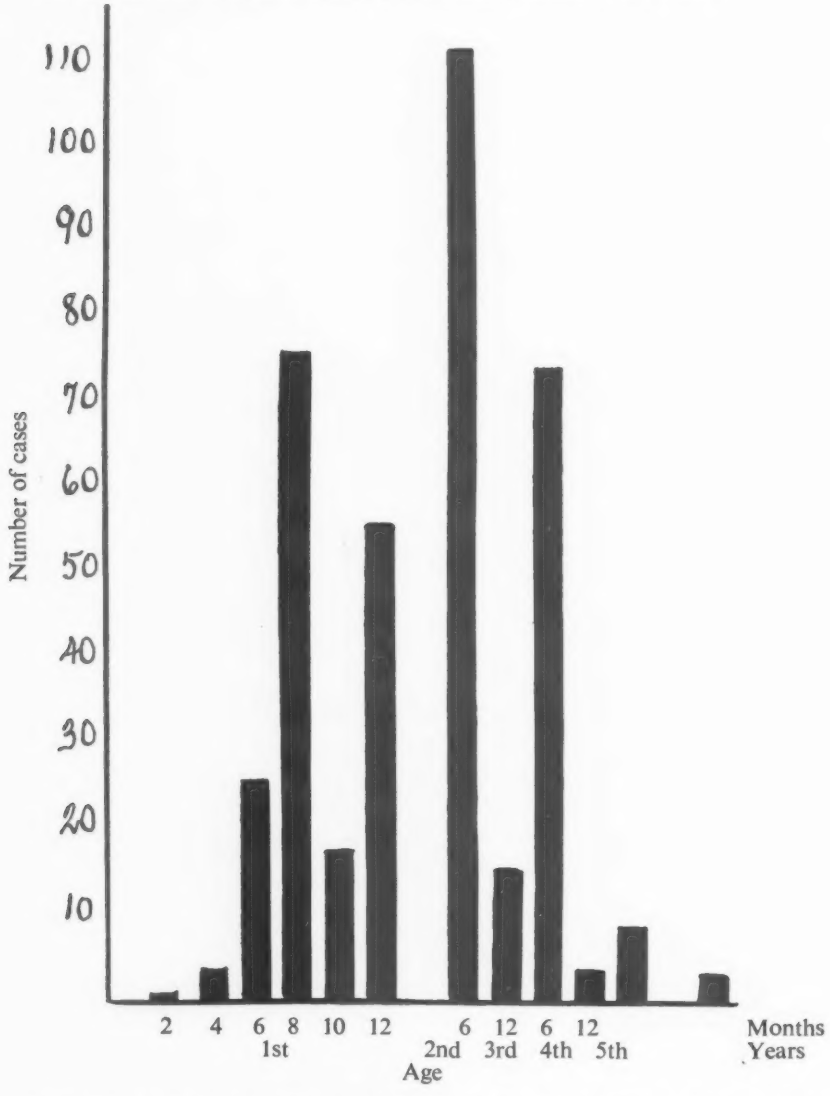


Baked rice cakes (sweetened) are made from roughly sieved, white, non-glutinous rice flour steamed, cut and then baked. Only a small amount of sugar is added. Ordinary starch cakes are made from rice flour, slightly steamed, but without the addition of sugar.

In addition to the points mentioned above in regard to breast feeding by the Chinese mother, the data in chart V show the ages at which breast feeding ceased in 398 cases.

CHART V

The distribution of ages at which breast feeding ceased in 398 cases



In nearly a third of the cases, breast feeding is discontinued by the end of the first year ; nearly half of all the cases continue into the second year ; a number continue until the end of the third year, and a few instances have been observed in which some feeding has continued until the end of the fourth and even fifth years.

Weaning

In a series of 305 cases, the indications for weaning were investigated. The results are shown in the following table :

TABLE 3

REASON GIVEN FOR WEANING	NUMBER OF CASES
Fresh pregnancy	153
Insufficient breast milk	49
'Child is big'	34
According to custom	23
Poor health of mother	19
Demands of employment	17
Poor health of child	3
Child refuses to take	2
Breast abscess	2
Fissured nipples	1
Uselessness of wet nurse	1
Doctor's advice	1

Enquiries showed that of 308 cases, 219 were weaned on to an adult diet. About half the remainder were fed largely on soft rice. In twenty-six cases milk powder was used. In only isolated instances was any addition of egg made, and only once was there a record of the use of soya bean milk.

Discussion

The feeding habits which have been described will be seen from table 1 to be mainly concerned with the natives of East-Central China. In general similar customs prevail in the predominantly rice-eating population of West-Central and South China. In the North, the staple cereals are millets and wheat. Methods of feeding of young children in North China have been described recently by Guy (1936). She says that infants are fed exclusively on breast milk until the age of six months, when tastes of the family food are introduced ; thus small amounts of soups made from turnip, cabbage or salted vegetable are fed along with a little gruel made from millet or rice and bits of steamed wheat bread, or one made from a mixture of corn flour and soya bean flour. Raw turnip is given to the child to nibble ; often some hot sweet potato, and rarely eggs.

It is noteworthy that, as in the present series, soya bean 'milk' is never used in infant feeding ; a hot weak solution sold in the streets of Peiping is taken by old people as a beverage. At a recent conference of nutrition experts in the Far East, it was recorded (Bandoeng Conference, 1937) that soya bean milk had little in common with mammalian milk beyond a white colour. A soft bean curd may, however, be used with advantage (Platt, 1936) in a mixture for weaning purposes.

Guy concludes that unless there is enough breast milk and until the child is able to feed without help, food is likely to be insufficient until about the eighteenth month. This is due not only to the expense and trouble involved in the preparation of special food, but also to a lack of patience at the inevitable slowness of the child. If, however, the child can be assured of a supply of 500–700 c.c. of maternal milk in addition to its share of the family diet, it is believed that the difficulties of this weaning period will be overcome.

King (1936) was told by a physician working in West China that there were many practices and customs which contributed to a high death-rate among Chinese infants. One of these was given as the feeding of meat masticated by the mother to children before they have teeth. This is said often to give rise to fatal convulsions in the infant. Pre-chewing of pap foods may be seen throughout China. It is known still to occur in other parts of the world—as, for example, in the Dutch East Indies, Indo-China, and parts of Africa. It was a custom in Europe, for, according to Still (1931), discussing conditions in the sixteenth century, ' writer after writer had handed on the unwholesome advice of Avicenna (980–1037 A.D.) that the nurse before giving bread or other solid food to the infant should chew it thoroughly in her own mouth, and then spew it, or put it with her fingers, into the infant's mouth.'

Additions of preparations of cereals to the infant's diet has, of course, been common for centuries in Western countries (Garrison, 1923 ; and Still, 1931). This practice led to the introduction of special utensils for feeding, the evolution of which has been described by Still. In China, chopsticks and porcelain spoons and bowls such as are used by adults are employed in infant feeding. In other countries spoons are not always available, so that when additions of gruels are made some other method is adopted. A description from Nyasaland (1938) is of interest in this connexion : ' The cupped hand is filled with gruel and attempts are made to empty the contents into the infant's mouth. Resistance is useless, the gruel flows down the nostrils and in the choking and spluttering which follows, a quantity is swallowed by the infant. This is repeated two or three times daily and sometimes at night.'

Whilst the use of rice in the parts of China investigated is determined by the fact that rice is the staple cereal, it is of interest to find that it has been recommended for use in infant feeding from time to time in the West. William Cadogan (1711–97) writes, ' I would advise therefore that one half of Infants Diet be light thin Broth, with a little Bread or Rice boiled in them which last is not so acescent as any other kind of Meal or Flour. . . .' It has long been recognized (Hutchison and Mottram, 1936) that rice is a most readily and completely digestible cereal. Of the cereals examined by E. Mellanby (1937) for their effect on the growth of bones, rice is the one which gives rise to the least adverse effect on calcification. The protein of rice, whilst only present to the extent of 7 or 8 per cent., is generally considered to be of good biological value. The inclusion of rice in the diets of mothers feeding babies, and into the diets of the babies has, on the other hand, been considered to have a deleterious effect on deciduous teeth, and the mortality and morbidity of infants, according to the results of an investigation by Larsen, Jones and Pritchard (1934) in Hawaii.

The Chinese use rice in a powdered form—the pulverization of the grain being a matter of some importance in determining utilization (Platt, 1936). They have also appreciated the advantage of thorough cooking of the cereal, for the rice starch cake is heated and partially dextrinized in course of preparation.

The fact, however, that rice is introduced into the diet so frequently and

at a very early age raises the question of digestibility of starch by the infant. There was a period in Europe after the general use of pap foods when breast feeding was insisted upon until the age of twelve months. More recently, feeds of starchy foods have been recommended to be introduced by some at six to eight months, and by others as early as the third or fourth month. One of the reasons given for not feeding starch during the first year was that the infant had no salivary enzymes capable of digesting the starch. There is, however, abundant evidence in the literature that there is ptyalin in the saliva of the infant and amylase in the pancreatic juice (Feldman, 1920 ; White House Conference, 1932–3). Whilst this is true, there is evidence that there is more ptyalin in strong than in weak infants, and that the amount of amylase increases markedly in older children. Furthermore, even when starch is properly prepared and well cooked, it is believed that the young infant cannot digest it completely, though it appears to be possible to develop gradually the power of digesting it fairly well when it is fed from an early age (White House Conference, 1932–3).

The problem of starch digestion has been recently discussed by Armand-Delille (1935). The results of the experiments of his assistants Bespaloff and Lestocquoy show that in infants under two months, amounts of 5–10 gm. of uncooked wheat flour fed with milk are not digested, and 5–10 gm. lots of fully cooked wheat flour are not absorbed ; from two to four months these amounts are partially absorbed, and after four months complete absorption may be obtained for both preparations fed at these levels. At this age, however, amounts of 15 gm. are incompletely digested. When the smaller amounts are fed daily for six to seven days, it appears that digestion becomes complete, and it is suggested that there is an adaptation taking place, probably in the nature of a progressive increase in the secretion of amylase. If pure wheat starch is used, it has been found possible to secure complete absorption of 30 gm. after feeding for fifteen days to a baby of three months.

From the present observations it appears that the Chinese have been feeding rice starch and flour in amounts similar to those found experimentally by the French investigators to be digested by young infants.

It is interesting that in the history of paediatrics systems of wet nursing similar to those in present use in China have been employed. The test of the quality of milk depending on the behaviour of a drop is similar to the ' finger-nail test ' used for centuries in Europe, and attributed to Soranus of Ephesus (98–117 A.D.). The accuracy of the Chinese gold balance is such that the specific gravity method is probably superior to those employed in early days in Europe.

The practice of irregularity of feeding both with regard to frequency and duration, the use of cathartics, and of worms, fish and wine extracts as lactagogues, have their counterpart in the history of infant management in Western countries. It should be emphasized that the Chinese are fully aware of the importance of adequate nutrition of the mother in pregnancy and throughout lactation.

The point was made at the beginning of this paper that a knowledge of

existing customs and circumstances must form the basis of any improvements. Only a superficial acquaintance with conditions in China will show that the introduction of Western methods is impracticable, for there is little milk except human milk, dairy farming requires too much land to be a practical measure, and the Chinese cannot, in general, afford to buy imported preparations of cows' milk. It is not proposed to discuss further this question of making improvements, except to quote a recent comment from a study (Buck, 1938) of 38,256 farm families in twenty-two provinces in China, in which is given a figure of 156 deaths under one year of age per one thousand births (an estimate which is probably low) : ' If, by some magic,' Buck writes, ' it suddenly became possible to eliminate the mortality from " preventable causes " of death, sober students might ponder long before utilizing that power. . . . It is perhaps fortunate that any improvement in mortality rates will, if it comes, come gradually, and may be accompanied by a corresponding decline in fertility.'

An outstanding feature in infant management, as in other aspects of Chinese domestic life, is a long-established tradition. This extends to the care given to children in the home. It has been considered in history (Garrison, 1923) that the status of the infant in society varies with that of the mother, and that therefore it is in the matriarchate in which the child is held in most esteem. Since Confucius the system in China has been maintained to be of the patriarchal type, but there is no question nowadays that considerable influence is exerted by women, especially by the lao-tai-tai (' old-great-great '—the master's mother, the matriarch). Before 200 B.C. there is said to have been no destruction of infants in China ; this is held to be accounted for by the existence then of mother authority. In other words, the Confucian idea of male sovereignty is associated with the abandonment or destruction of infants, especially the female, under the stress of famine or war, the child being regarded as a subject or chattel. Whilst this may be the case, it is a matter of common observation that in ordinary circumstances the Chinese treat their children kindly and well.

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NUTRITIONAL ANAEMIA IN AN INDUSTRIAL DISTRICT *

BY

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The incidence of nutritional anaemia in infancy has aroused considerable interest in recent years, and its recognition and proper treatment are matters of national concern. Since attention was drawn to the frequency of this form of anaemia during infancy by Mackay (1931) many workers have studied the problem, mainly from the aspects of diagnosis and treatment. Apart from the work of Mackay, there have been few investigations into its incidence in this country (Davidson *et al.*, 1935 ; Findlay, 1937 ; Fullerton, 1937 ; Colver, 1938). It is important that this aspect be further studied, partly because of its importance in the social welfare of the infant and partly because of the light it throws on the etiology of iron-deficiency anaemia as a whole.

The present investigations were made to determine the incidence of the iron-deficiency anaemia of infancy in a large industrial area of Glasgow. Haemoglobin estimations were made on 300 infants of all ages up to one year. These infants were all under the supervision of a Welfare Clinic in Govan, a densely populated district. They did not receive iron supplements to their diets, and were regarded by their mothers as healthy. The haemoglobin estimations were all carried out by the same observer, using a standardized Haldane haemoglobinometer. The blood was taken from the heel, the same two-edged stilette being used for every case.

The present results have been compared with the curve suggested by Mackay (1931, 1933*a*) as representing the normal haemoglobin levels for the first year of life. The figures given by Mackay for normal values were obtained as follows : the values at two weeks to one month, one to two months and two to three months were averages for groups of breast-fed babies living in their own homes ; those for three to four months of age and upwards were based on haemoglobin values obtained with iron treatment, because it was assumed that these values would more truly represent the optimum than the lower values obtained at this age from babies without treatment. Josephs (1936) criticizes the view of Mackay (1931) that merely because iron raised the haemoglobin level, values below this should be regarded as indicative of iron deficiency. An effective reply would seem to be that not only does iron raise

* This work was carried out during the tenure of a McCunn Medical Research Scholarship.

the haemoglobin level, it also diminishes the incidence of infection and increases the average gain in weight (Mackay, 1928) ; in short, it assists in the maintenance of perfect health. Furthermore, the curve obtained by Merritt and Davidson (1933) from haemoglobin values obtained from babies in New York City (where there is apparently little tendency for infants to become anaemic) is 'strictly parallel' to Mackay's standard normal haemoglobin curve.

Results of investigation

In fig. 1 the results obtained in the present series of 300 infants are presented. The individual estimations are plotted in relation to Mackay's normal haemoglobin curve. The well-known trend of the haemoglobin level, which falls rapidly during the first two months of life, is clearly shown ; it should also be noted that the majority of haemoglobin estimations during the first ten weeks of life fall into close proximity to the normal curve for that period. From the fifth month onwards, however, the individual values with few exceptions fall below the normal, frequently by as much as 15 to 30 per cent. This high incidence of anaemia among infants of the working class agrees closely with the findings of other workers in this country (Fullerton, 1937 ; Mackay, 1931 ; Colver, 1938). In fig. 2 is shown the average haemoglobin value at each month of age of the 300 infants studied. During the half to one month age period the haemoglobin percentage averages 100·5 per cent. ; it falls rapidly, maintaining a close relationship to the normal curve, so that by two to three months it reaches 72·5 per cent. For the next three months it rises slightly, reaching an average level of 75·6 per cent. at five to six months old. Thereafter it drops slowly to 71 per cent. at nine to ten months and is constantly more than 10 per cent. below the normal value of 86 per cent. These graphs show in a striking manner that it is only after the first six months of life that anaemia becomes so common. Taking a haemoglobin level of 10 per cent. or more below Mackay's normal as indicating anaemia, only 25·3 per cent. of infants under three months and 25·3 per cent. in the three to six month age period appeared to be anaemic, while in the age periods six to nine months and nine to twelve months, 70·7 per cent. and 70·0 per cent. respectively showed anaemia. These results are similar to those of Mackay (1933*a*) and Fullerton (1937). They differ from those of Findlay (1937), who found no evidence of anaemia in sick children in the East End of London. Findlay's cases, however, were hospital patients including probably many who were under weight and in whom the haemoglobin values were likely to be higher than in rapidly growing infants of the same ages.

The present series contains no haemoglobin values for the first two weeks of life. It is known, however, that the haemoglobin level is high at birth—143 per cent. (Mackay, 1933*a*) ; thereafter it falls rapidly till it reaches 106 per cent. at half to one month. This fall is the result of haemolysis in response to the sudden rise in oxygen tension of the infant's blood at birth (Mackay, 1933*b*), when the lung takes the place of the placenta as a medium of oxygenation.

As has been noted, the haemoglobin level continues to fall until about the third month of life, in some cases reaching remarkably low levels (fig. 1). There

HAEMOGLOBIN PERCENTAGE IN 300 INFANTS REFERRED TO AGE

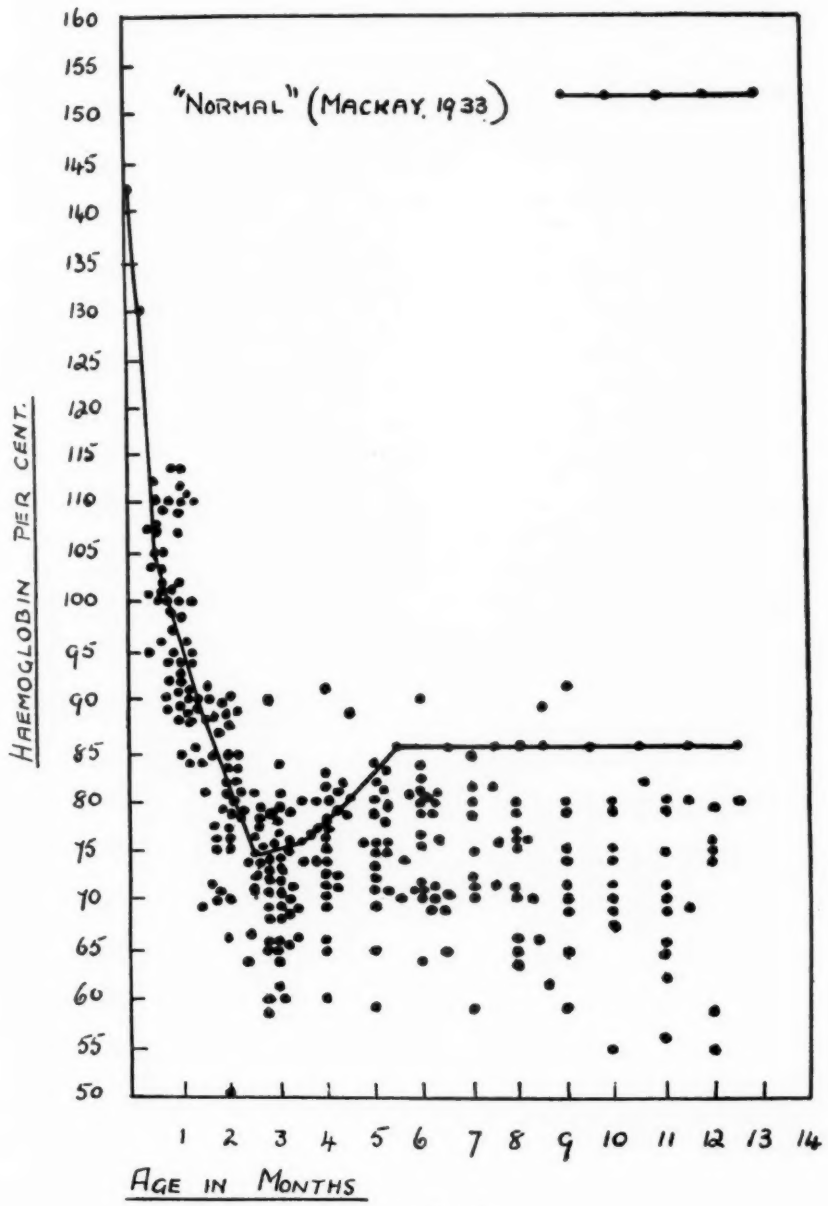

FIG. 1.

AVERAGE HAEMOGLOBIN VALUES FOR EACH MONTH OF THE FIRST YEAR OF LIFE

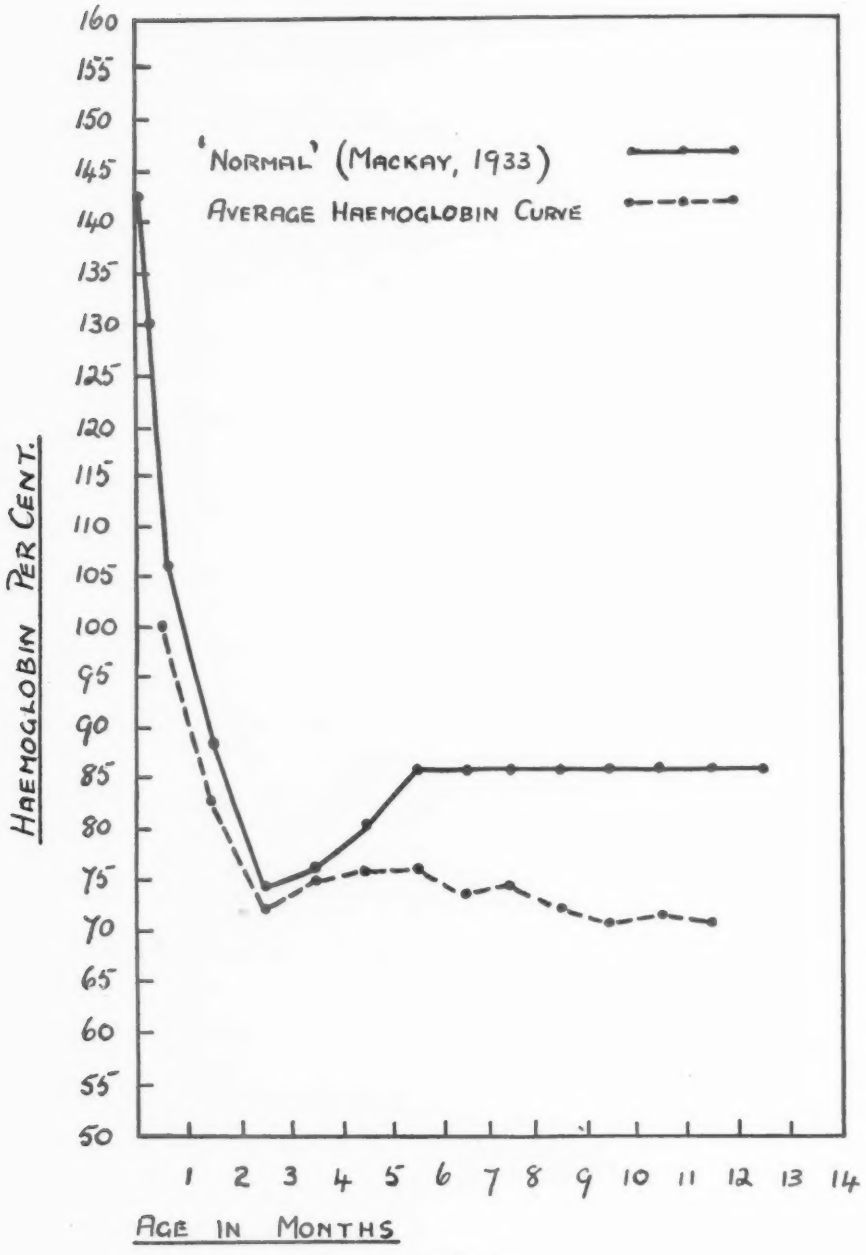

FIG. 2.

appears to be little doubt that this fall is due to continued haemolysis and must be considered physiological. That iron deficiency does not play a part is shown by the following facts :

(1) Iron does not prevent the fall in haemoglobin during the first three months (Mackay, 1933*b*) ; (2) the iron content of the liver increases up till the age of two months (Gladstone, 1932) ; (3) the reductions in red cells and haemoglobin are parallel and the blood does not show the low colour index of iron deficiency (Merritt and Davidson, 1933) ; (4) if iron deficiency were a factor, then babies who grow most rapidly would show the lowest haemoglobin levels, which is in fact not the case (Mackay, 1931). Hampson (1928) found an excessive bilirubinaemia until one month of age, and suggests that the haemolysis in the early weeks of life is controlled by the presence of an anti-haemolytic hormone. Josephs (1932), however, regards the fall in haemoglobin to be due to diminution in the rate of haematopoiesis rather than to increased destruction of the blood, putting forward as evidence the fact that administration of iron during the first three months of life has no influence on the reticulocytes, nor is it capable of arresting the fall in haemoglobin and red cells. Of possible significance in this connexion is the finding of Trought (1932) that in the placenta and blood of the new-born infant there is a proportion of haemoglobin differing in some way from that of the adult. This ' haemoglobin-alpha ' persists in the circulation at least till six weeks, i.e. during the time of the most rapid fall in haemoglobin. It is not known if this ' haemoglobin-alpha ' has any effect on the resistance of the red cells to haemolysis. Of some interest is the finding (table 1) that by two to three months it is in babies of low birth weight that the haemoglobin has fallen to the lowest levels, in spite of the fact that the lower the birth weight the higher the average haemoglobin level at birth (Mackay, 1933*b*). Thus babies of the lowest birth weight have the most rapid falls in haemoglobin values during the early months.

TABLE 1

AVERAGE HAEMOGLOBIN VALUES FOR FIRST YEAR OF LIFE REFERRED TO BIRTH WEIGHT

BIRTH WEIGHT, IN POUNDS	½–1 MTH.	1–2 MTH.	2–3 MTH.	3–4 MTH.	4–5 MTH.	5–6 MTH.	6–7 MTH.	7–8 MTH.	8–9 MTH.	9–10 MTH.	10–11 MTH.	11–12 MTH.
Under 4 ..	—	—	71·0	—	—	—	—	—	—	—	—	—
,, 5 ..	96·0	79·3	65·0	68·0	—	68·0	—	—	—	74·0	—	—
,, 6 ..	89·5	66·0	69·2	66·0	58·0	67·0	58·0	—	72·0	—	—	—
,, 7 ..	102·3	81·7	72·5	76·0	73·3	75·8	65·0	—	58·0	68·0	77·5	72·0
,, 8 ..	98·6	82·6	72·1	78·1	76·8	77·0	78·5	74·6	68·6	69·8	71·3	68·3
Over 8 ..	104·0	85·1	74·1	73·1	77·2	77·0	75·1	73·6	79·8	72·7	70·5	74·0

A likely explanation of the rise in haemoglobin values between the third and sixth months (fig. 2) has been given by Gladstone (1932). He found that the iron content of the liver increased steadily till the age of two months while haemolysis was in progress. Thereafter it diminished, until at four months it had returned to the birth level. This is taken to indicate that after the age of two to three months, when haemolysis is at an end, the stored iron is released for haemoglobin formation, and that this store is exhausted about the age of six months, after which time iron-deficiency anaemia begins to appear. Mackay

(1931, 1933*a*) has shown that the administration of iron can produce a higher average value at four months than that obtained in the present series (fig. 2), which suggests that sometimes the need for extra iron occurs as early as three months.

Following the slight rise in haemoglobin values during the third, fourth and fifth months the curve falls gradually (fig. 2). On the other hand, the administration of iron from the age of two months produces an average haemoglobin value of 86 per cent. (Mackay, 1933*a*) throughout the second six months of life, and the infants so treated show a lower morbidity rate. In view of these facts there can be little doubt that the low values obtained in the present series for infants over five months of age (fig. 1) find their explanation in a deficiency of iron. There remains to discuss the explanation of this deficiency.

Causes of iron deficiency

Deficient ante-natal storage of iron.—It is the view of many workers that though the foetus is able to draw upon the mother for all blood-forming materials for its own immediate needs, irrespective of the condition of the maternal blood, infants born to anaemic mothers are unable subsequently to maintain a normal haemoglobin level during the first year of life (Strauss, 1933 ; Mackay, 1931 ; Paxton, 1936). The Birmingham workers are of the opinion that ante-natal storage of iron may be deficient to such a degree as to produce a congenital nutritional anaemia (Parsons, 1932 ; Parsons and Hawksley, 1933). This opinion appears to be based entirely on a history, from the mothers, of pallor at birth and on ability to produce an iron-deficiency anaemia in the new-born rat (Parsons and Hickmans, 1933). They put forward the suggestion that some mothers, who may not themselves exhibit hypochromic anaemia, have the power to retain their iron to the detriment of the foetus (Neale and Hawksley, 1933). Most authorities agree, however, that the haemoglobin level at birth bears no relation to maternal anaemia. Acting on this assumption and considering iron-deficiency anaemia from a quantitative aspect, Fullerton (1937) has concluded, from a convincing series of calculations, that the iron content of the new-born infant is independent of that of the mother. The same worker in a previous paper showed that the iron drain by the foetus is not sufficiently large to cause a marked effect on the maternal iron content (Fullerton, 1936).

Deficient post-natal supply.—It is generally agreed that the iron content of cow's milk is lower than that of breast milk (Peterson and Elvehjem, 1928 ; Cunningham, 1931 ; Wallgren, 1932), although there is marked variation in the figures obtained by different workers and conclusions based on this supposition have as yet but poor foundations. Nevertheless in the present series the average haemoglobin curve obtained from breast-fed infants shows constantly higher values than the curve of the bottle-fed infants save for the five to six months age period (fig. 3). The average value for the eight to nine months age-period in the breast-fed group is seen to be 81 per cent. ; this figure is probably erroneous, as only two of the breast-fed infants fell into this age group. This

AVERAGE HAEMOGLOBIN VALUE OF BREAST-FED INFANTS COMPARED WITH VALUES FOR ARTIFICIALLY-FED INFANTS.

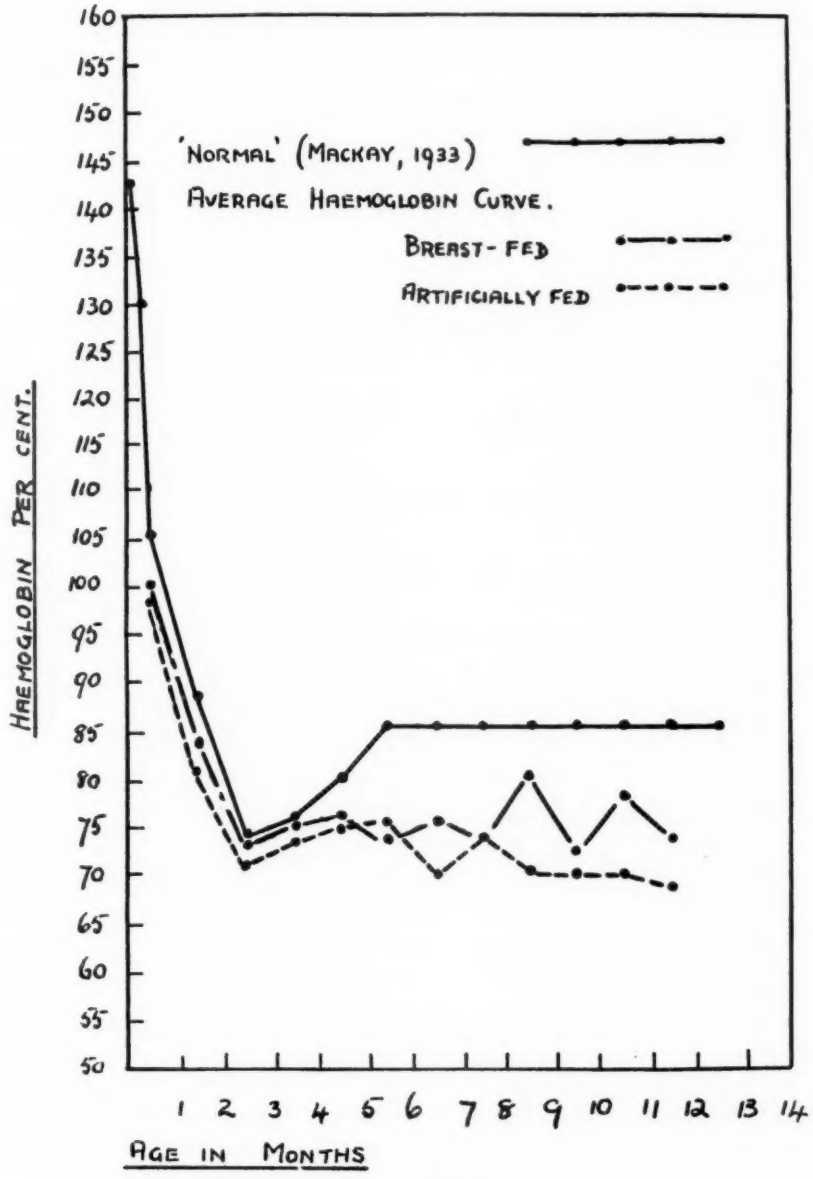

FIG. 3.

difference between the breast-fed and bottle-fed infants is less marked in the present series than was found by Mackay (1931) and Fullerton (1937). Although it has been suggested that the relatively high values found in the breast-fed infants are due to the higher iron content of human milk, it should be noted that this hypothesis does not explain why the bottle-fed infants showed lower values as early as the age of half to one month, a time when the administration of iron does not affect the fall in the haemoglobin content of the blood. A possible explanation lies in the fact that in the present series there were more premature babies and infants of low birth weight (under 6 lb.) in the first three months than during the rest of the year, and it is known that such babies have a more rapid fall in haemoglobin, are more likely to be bottle-fed, and have a lesser expectation of continued life. For this reason the curve for bottle-fed infants under three months was made up from a group containing more prematures and infants small at birth than the group of breast-fed infants. Consequently the haemoglobin curve of the bottle-fed group tends to be lower than that of the breast-fed group. Josephs (1934) found a positive iron balance of about 6 milligrammes per month in bottle-fed infants, and calculated that an exclusive milk diet cannot cause anaemia on the basis of its low iron content alone. Langstein and Edelstein found a similar retention of iron in infants fed on human milk. It would however seem that, although the low iron content of milk, prolonged milk feeding and delayed institution of mixed feeding are likely to be potent factors in the production of iron-deficiency anaemia, there is little evidence to explain why the bottle-fed infant should have a greater tendency to become anaemic than the breast-fed infant. At the same time the present results (fig. 3) and those of others clearly demonstrate that this tendency is in fact present, and it is only possible to conclude that the anaemia is dependent in part on factors influencing iron utilization or iron storage which are not yet understood.

Birth weight.—It was found in the present series (table 1) that during the second half of the first year of life, infants of low birth weight had on the whole a lower haemoglobin level than infants weighing 7 lb. and upwards at birth. This finding is in agreement with those of other workers (Kunckel, 1915 ; Mackay, 1931 ; Abt and Nagel, 1932 ; Magnusson, 1935 ; Fullerton, 1937). The frequency of nutritional anaemia in premature infants and twins (Parsons and Hawksley, 1933) is a direct consequence of low birth weight. The tendency for the development of iron deficiency in infants small at birth depends on the fact that infants of low birth weight grow more rapidly in relation to birth weight than infants of normal weight, having at the same time a lower absolute iron content because of a smaller blood volume and a lesser iron store in the liver. The correlation between the haemoglobin level and the rate of growth has been stressed by Mackay (1931), Josephs (1934) and Fullerton (1937). This also applies to premature infants and twins. It has been frequently stated that as deposition of iron in the liver occurs most rapidly in the last three months of gestation (Hugounenq, 1899), early exhaustion of the foetal stores of iron explains the frequency of anaemia in premature infants in whom the period of iron storage has been cut short, and in twins in whom the available iron has to

be shared. Gladstone (1932) has pointed out, however, that although the acquisition of iron by the foetus is greater during the last four months of intra-uterine life than during the first six, the foetal gain in weight during the last three months is greater than during the first seven. Thus during foetal life the increase in total iron content is not more rapid than the increase in total weight, so that premature babies are in relation to their weight almost as well supplied with iron as the full-time baby. It would appear that the greater tendency for anaemia to develop in babies small at birth is the result of relatively rapid growth in weight together with excessive haemolysis in the first two to three months of life (vide supra).

Infections.—The occurrence of a hypochromic anaemia in association with acute and chronic infections is well recognized (Collins, 1935 ; Minot and Heath, 1932 ; Sturgis et al., 1935 ; Vaughan, 1936). Fullerton (1937) and Josephs (1934) are of the opinion that infection is an important etiological factor in the iron-deficiency anaemia of infancy. In table 2 are found the average haemoglobin values in the present series arranged according to whether or not there was a history of infections. The infections comprised mainly mild gastro-intestinal and respiratory diseases and the exanthemata. Fifty-five per cent. of the infants had a history of one or more infections. It is seen that there is little difference in the haemoglobin values of the two groups, a result which at first appears surprising. The figures cannot be taken as reliable, however, as the histories of the infections were obtained from the mothers who were not all of average intelligence. Attacking this problem from another aspect, the author has found that severe infections have an adverse influence in the utilization of iron for haemoglobin synthesis (unpublished), and that severe illnesses are frequently followed by anaemia. Mackay (1928) has observed an increased susceptibility to infections on the part of anaemic infants, and it seems probable that in this way a vicious circle may be established—infection causing anaemia and anaemia predisposing to infection. Fullerton's (1937) results leave little doubt that infections may cause marked falls in the haemoglobin level even during iron therapy.

TABLE 2

AVERAGE HAEMOGLOBIN VALUES ACCORDING TO HISTORY OF INFECTIONS

	5–6 MONTHS	6–7 MONTHS	7–8 MONTHS	8–9 MONTHS	9–10 MONTHS	10–11 MONTHS	11–12 MONTHS
No history of infections	76	75	71·6	72	67·8	72·2	71
History of infections ..	74	73·5	75	72·9	73·6	71·7	72·5

Prophylaxis

In view of the high incidence of iron-deficiency anaemia in working-class infants the desirability of its prevention must be stressed, not so much on account of the anaemia per se but because of the associated high morbidity and mortality

rates. Mackay (1931) has found the administration of 4½–9 grains of ferri et ammon. citras daily from the age of two months an effective measure in preventing anaemia and diminishing the incidence of infections. Alternatively, a dried milk to which iron has been added may be used. Others have tried a more natural but effective prophylactic agent in the addition of foods of high iron content to the infants' diet at a more early age than has been customary in this country (Whitby and Britton, 1935). At the age of four to five months broth, vegetable purée and the yolk of an egg may be added without harmful effect. It would be good if this method of early 'mixed' feeding could be widely adopted.

Summary

1. A study of 300 infants provides evidence of the prevalence of iron-deficiency anaemia during the first year of life. Twenty-six per cent. of the total number of breast-fed infants and 35 per cent. of the bottle-fed infants gave haemoglobin values of at least 10 per cent. below Mackay's normal values for their respective ages. These percentages become much greater if infants under the age of six months be excluded.

2. The principal factors influencing the development of this type of anaemia are discussed. They are: (1) undue prolongation of exclusive milk diet; (2) low birth weight; (3) infections.

3. The importance of prophylaxis is stressed and methods of effecting this are discussed.

Thanks are due to the Managers of the Govan Welfare Centre, who provided the facilities for this work, and to the Medical Research Council, who defrayed part of the expenses.

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CASE REPORTS

GANGRENE OF THE EXTREMITIES IN AN INFANT

BY

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Case record

One of twins, a girl aged eleven weeks, was admitted to Llandough Hospital on December 28, 1937, because of feeding difficulties. She was born a month prematurely after a normal confinement, and her birth weight was 4 lb. 6 oz. Her twin, also a girl, was admitted at the same time with a similar complaint. This baby was discharged after three weeks in hospital, having made good progress. The history of the patient here discussed was that she had been breast-fed for three weeks and then weaned under the impression that 'the breast milk was not agreeing with her.' She was given a half-cream dried milk and later a 'humanized' dried milk. There had been occasional vomiting, the stools were constipated, and she was not gaining weight, which on admission was 4 lb. 8 oz.

When first seen she was a little wasted, with some dehydration, and was put on a 'humanized' dried milk with dextri-maltose, and she started to improve in her general condition and her weight began to go up. Ten days after admission the temperature suddenly rose to 104° F. in the rectum and she became fretful. A red area developed over the right side of the face and ear with a well-marked raised edge, and she was transferred to the Cardiff City Isolation Hospital at thirteen weeks old with erysipelas.

Whilst in the Isolation Hospital she was given sulphanilamide, a quarter of a 5-grain tablet three times a day, with rapid improvement, and was re-admitted to Llandough Hospital after four days, with no areas of redness, but a little oedema of the scalp on the right side. Her temperature was normal and her general condition had improved. Two days afterwards a small localized abscess developed over the right parietal bone, and a day later similar swellings appeared on the dorsum of the left foot, over the proximal phalanx of the third finger of the right hand, and the proximal phalanges of the index and third fingers of the left hand. The abscesses on the dorsum of the foot and on the scalp were incised and thick whitish pus obtained, which grew non-haemolytic streptococci with no viridans reaction. The other septic areas were not incised and healed in about two to three weeks with the exception of the right index finger, which remained swollen, but not tender or fluctuant, for some weeks. The temperature showed an occasional rise to 99°–100° F. throughout this period, but the child gained weight slowly and took her feeds well.

On March 8, i.e. at twenty-two weeks old, both feet were noticed to be

cyanosed, especially the toes, and there were small purpuric spots in the pulps of all the toes and extending along the terminal quarter of an inch of each toe. The skin was warm to the touch in both feet and the dorsalis pedis artery pulsating. The tips of the fingers of the left hand and the little fingers of the right hand were similarly affected. On the following day the hands and feet were much the same, but a small purpuric area was present on the tip of the nose. During the next day or so the cyanotic area seemed to be spreading up the fingers of the left hand and the second, fourth and fifth fingers of the right hand. Meanwhile the skin had developed a scaly eczematous rash mainly on the trunk and scalp, with a number of primary intradermal pustules. Induced hyperaemia by manual compression of the limbs increased the cyanosis, and

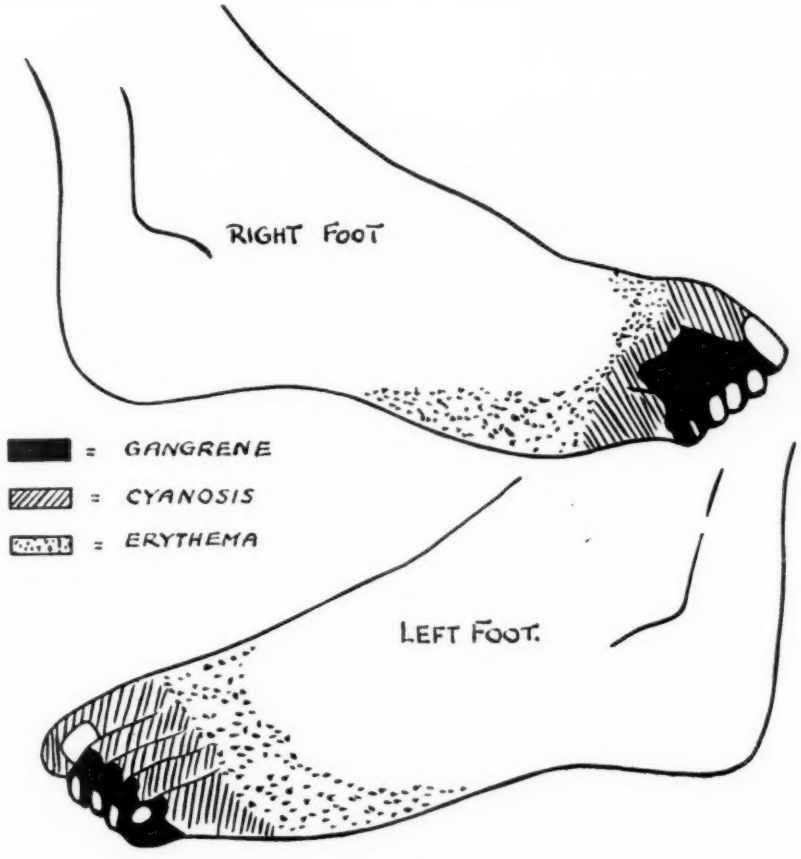

FIG. 1.

when the pressure was released the capillaries dilated well except at the extreme tips of the fingers and toes. Fourteen days after the onset of the cyanosis the middle toes of both feet became gangrenous, to be followed by gangrene of other toes, with clear lines of demarcation at the base of the gangrenous areas. On March 24, at the age of twenty-four weeks, the condition of the extremities was as follows :

Right foot : Tip of big toe gangrenous with cyanosis as far as the base. Second and third toes gangrenous to the base. Tip of little toe gangrenous, with cyanosis as far as the base. The cyanosed areas extended a little beyond the base of the toes, and proximal to this was a zone of

erythema extending about half an inch along the dorsum of the foot, and rather further along the outer edge and sole.

Left foot : Tips of second, third, fourth and fifth toes gangrenous extending to level of terminal interphalangeal joint with cyanosis of all toes as far as their bases. An erythematous zone extended along the dorsum of the foot and outer side similar to that on the right foot.

Right hand : Cyanosis of fingers and thumb as far as level of distal interphalangeal joint, except of little finger, where the cyanosis extended to the base, and continued into an area of erythema.

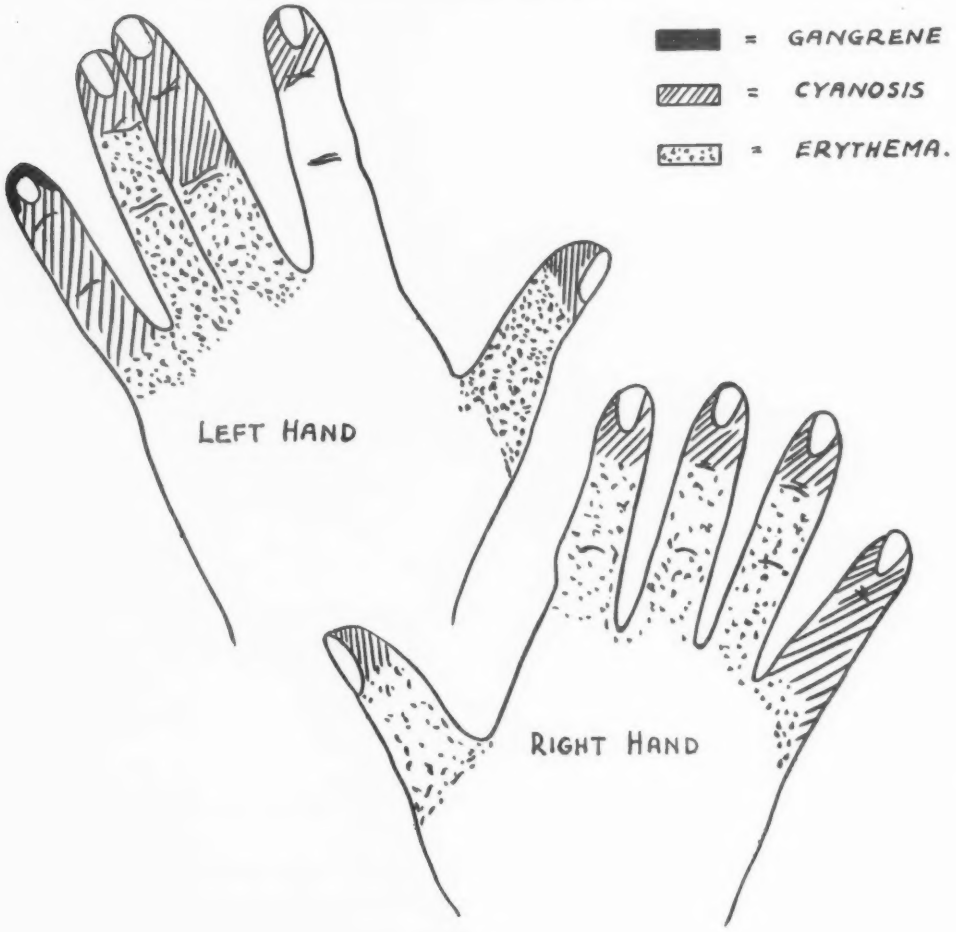

FIG. 2.

Left hand : Cyanosis of tips of thumb, second and fourth fingers as far as level of proximal joint, and of the little finger as far as the base, with gangrene at the tip of this finger. The thumb, third and fourth fingers were erythematous to their bases beyond the cyanotic zones (see fig. 1 and 2).

Throughout this period the child's condition remained amazingly good. She took her feeds well, gained weight slowly and had no digestive disturbances. The eczematous condition of the skin improved with treatment, and it was with disappointment that there was found, fourteen days after the onset of the

gangrene, a blood-stained nasal discharge which gave a positive virulence test for diphtheria. She was again transferred to the Cardiff City Isolation Hospital, where she remained for two months and progressed well, gaining from 6 lb. 7 oz. to 9 lb. 6 oz. While there the toes separated at the lines of demarcation without any signs of sepsis, and on re-admission to Llandough Hospital at the age of seven months her condition was good, though she was still under normal weight. The state of her hands and feet was as follows :

Right foot : Big toe, gangrenous tip separating. Second toe separated at level of distal interphalangeal joint. Third, fourth and fifth toes separated at level of proximal joints.

Left foot : Big toe, normal. Second, third and fifth toes separated at level of proximal interphalangeal joint. Fourth toe separated at level of distal joint.

Right hand : normal.

Left hand : normal except for loss of small area of pulp of the little finger.

Treatment.—Feeds of ' humanized ' dried milk with dextri-maltose were continued throughout. Iron and a vitamin A and D concentrate were also added. The eczematous condition was treated by bathing with lot. hydrarg. perchlor. 1 : 4000 and calamine lotion. For the nasal diphtheria 14,000 units of anti-diphtheric serum were given. As soon as the cyanosis was discovered the hands and feet were wrapped in cotton-wool and the limbs kept as warm as possible with hot bottles. No wet dressings were applied at any time and a simple dusting powder was used. Hyperaemia was induced by repeated manual compression on the forearms and legs. A better reaction was invariably obtained in the upper than the lower limbs. This method was continued until the onset of gangrene. When in the Isolation Hospital for erysipelas she was given a quarter of a 5-grain tablet of sulphanilamide three times a day, and on return to Llandough Hospital another form of this drug was given in a dose of a quarter of a $3\frac{3}{4}$-grain tablet three times a day. This was continued for a month until the onset of cyanosis, but no untoward general symptoms were noted attributable to its use.

Investigations.—Blood counts showed no gross abnormality at any time beyond a slight secondary anaemia. During the purpuric and early cyanotic stage the following figures were obtained :

Blood platelets : 180,000 per c. mm.
Bleeding time : 100 seconds.
Coagulation time : 45 seconds.

The Wassermann reactions of mother and child were both negative.

Culture from the pus grew non-haemolytic streptococci, not of the viridans type.

Discussion

An unexpected clinical feature was the slight general disturbance throughout. Gain in weight was slow, but there was no loss in weight at any time, and the infant always took her feeds well with no digestive disturbances ; all this in spite of gangrene, erysipelas, eczema and a virulent nasal diphtheria !

Gangrene in an infant is a rare event. Dohen (1934) published an example of gangrene in a new-born infant and reviewed the literature of the condition in the newly born. He was unable to arrive at any definite etiological cause, and only one case was associated with sepsis—in the umbilicus. A patient who

developed gangrene on the seventeenth day showed at autopsy a thrombosis of both anterior and posterior tibial arteries with ' mediitis of both arteries ' histologically. Other causes of gangrene in infancy that have been recorded are those associated with congenital syphilis (Bloise, 1936), diabetes (Lawrence and McCance, 1931) in association with severe infectious fevers and in pink disease (Rocaz, 1936).

So far as the present case is concerned, congenital syphilis was excluded serologically by a negative Wassermann reaction in both mother and child, and clinically by the absence of any other signs of syphilis, and the normal twin sister. Nasal diphtheria developed after the onset of gangrene and the child's condition was so good throughout that it can hardly be considered a possible factor.

It would appear from the facts of the case that the likely cause for the production of the gangrene was an arteritis produced by the streptococcal infection and leading to thrombosis of the phalangeal arteries, and that rupture of affected capillaries led to the purpura. The presence of dry gangrene throughout and the response to hyperaemia suggested a thrombotic process and not an embolic one, since the latter would probably bring infection to the site of lodgement. Moreover, the absence of any central focus of infection and the good condition of the infant were against an embolic phenomenon. An exact proof of a streptococcal arteritis cannot of course be offered, but it is felt that this theory offers the best explanation of the findings. In view of the prolonged use of sulphanilamide it is natural to wonder if it may not have taken some part, but no reference can be found to thrombosis or gangrene following its use.

Acknowledgements

Thanks are due to Dr. Emrys Harries, Medical Superintendent, Cardiff City Isolation Hospital, for permission to use his records and for the care he took of the child, and to my house physician, Miss Catherine Howell, for her note-taking and the time and attention she gave to the baby.

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CONGENITAL MITRAL STENOSIS

BY

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Congenital mitral stenosis is a rare malformation of the heart and is nearly always associated with other anomalies in the heart or vessels.

Cowan and Ritchie (1935) found no example in their post-mortem series of 101 cases of chronic mitral valvular disease, but Farber and Hubbard (1933) report three out of fourteen cases of foetal endomyocarditis. In Maud Abbott's (1931) series of 1,000 cases of congenital heart disease twenty-three were present, of which only six could be classified as the primary lesion, the remainder complicating other grosser defects. Analysing these six cases, Maud Abbott found the average age to be five-and-a-half years and the oldest twenty-seven years. The commonest associated anomaly was a patent ductus arteriosis with hypoplasia of the aorta. Cyanosis was variable and dyspnoea a common symptom ; clubbing was detected only in one, but delayed development in four out of the six cases. The physical signs were variable, the commonest being an apical systolic murmur. In only one case was the full picture of thrill and pre-systolic murmur detected. Death was commonly of sudden onset and post-mortem examination revealed hypertrophy of the right side of the heart.

Investigation of the post-mortem records of the Hospital for Sick Children, Great Ormond Street, dating from 1860 (see table) showed 250 cases of congenital heart disease, seven of which revealed stenosis of the mitral valve. In only one case could it be described as the primary lesion (Newns, 1938), this showing the characteristic enlarged left auricle and right side of the heart. There was no other congenital defect, death being due to sudden collapse after a blood transfusion. Of the remaining six cases, two showed an aplasia of the whole of the left side of the heart ; one an undeveloped left ventricle with patent ductus arteriosis ; one was associated with a large patent interventricular septum, and two with tricuspid stenosis and evidence of foetal endocarditis in the form of a fringe of vegetations on the valves. It is interesting to note that the average age in this series of cases was six months and 86 per cent. were male infants.

ANALYSIS OF SEVEN CASES OF CONGENITAL MITRAL STENOSIS FROM THE POST-MORTEM RECORDS OF 250 CASES OF CONGENITAL HEART DISEASE AT THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET, FROM 1860–1938

CASE	AGE	SEX	DEGREE OF MITRAL STENOSIS	ASSOCIATED ANOMALY	PREDOMINANT LESION	SIZE OF CARDIAC CHAMBERS	CARDIAC SIGNS	MISCELLANEOUS	CAUSE OF DEATH
*1	1 yr. 9 mth.	M.	Advanced.	Bicuspid aortic valve.	Mitral stenosis.	L. auricle hypertrophied and dilated. Pulmonary artery dilated. R. ventricle hypertrophied.	Loud 1st sound. Pre-systolic murmur at apex.	Anaemia. Dyspnoea. No cyanosis or clubbing.	Sudden collapse after blood transfusion.
2	4 mth.	M.	Advanced.	Aplasia of left side of heart.	Aplasia of left side of heart.	L. auricle thin, small. L. ventricle small. R. auricle dilated, hypertrophied. R. ventricle ditto.	Loud 1st sound. Short pre-systolic murmur at apex.	Dyspnoea. Cyanosis.	Diarrhoea and vomiting.
3	10 mth.	M.	Advanced. Circumference 1¼ inches.	Aplasia left side of heart. Patent ductus arteriosis.	Aplasia left side of heart.	L. auricle small. L. ventricle ditto. Pulmonary artery dilated. R. ventricle hypertrophied.	Apical systolic murmur.		Acute bronchitis.
4	4 days	M.	Advanced.	Small L. ventricle. Patent foramen ovale. Bicuspid aortic valve. Small ascending aorta. Patent ductus arteriosis.	Aplasia of left ventricle.	L. auricle normal. L. ventricle very small. R. auricle dilated. R. ventricle dilated and hypertrophied.		Cyanosis.	Collapse of left lung with effusion.

* To be published later.

5	14 wk.	F.	Moderate.	Interventricular septum almost absent. Patent foramen ovale.	Patent.	L. auricle hypertrophied and dilated. R. ventricle very small.		Cyanosis. Dyspnoea.	Broncho-pneumonia.
6	3 mth.	M.	Moderate. Fringe of vegetations.	Pulmonary stenosis. Tricuspid stenosis. Patent interventricular septum. Patent foramen ovale. Patent ductus arteriosis.	Pulmonary stenosis.	L. auricle normal. L. ventricle dilated and hypertrophied. R. auricle dilated. R. ventricle ditto.	Blowing systolic murmur at mitral and tricuspid areas.	Cyanosis. Dyspnoea.	Cause not stated.
7	2 mth.	M.	Moderate. Seat of old endocarditis.	Tricuspid stenosis. Patent interventricular septum. Patent ductus arteriosis.	Tricuspid stenosis.		Loud bruit all over chest.		Broncho-pneumonia.

FIG. 1.—Electrocardiogram 1935.

FIG. 2.—Electrocardiogram 1938. Some R. ventricular preponderance. Sharp P waves in leads 1 and 2, inversion of P in lead 3. Well marked Q waves in leads 2 and 3. Lead 4 is normal.

Case record

HISTORY. A male child aged six years and four months was first sent to the Out-patient Department at Great Ormond Street with the history of coughing since birth and repeated vomiting. He had also had attacks of panting and turning purple over the forehead. Delivery was normal but three weeks premature, and the mother states that when three months pregnant she had a severe shock with a gas explosion. Birth weight was 5 lb. 10 oz. and the child was breast fed for four months. At three weeks jaundice was first noticed and persisted until four months old, followed by an attack of

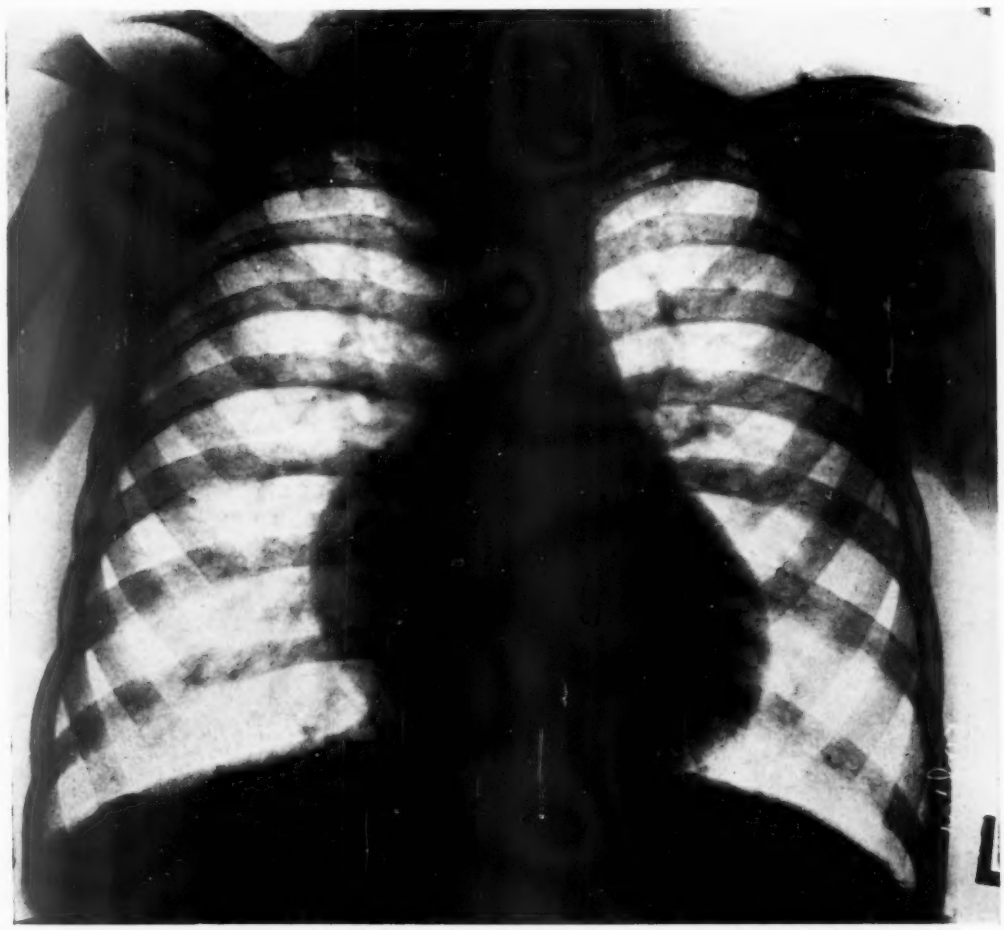

FIG. 3.—Antero-posterior X-ray of the heart showing enlargement of the right side.

gastro-enteritis and later marasmus for which he was treated in several hospitals. It was at this time that signs of congenital disease of the heart were first detected with a systolic thrill and bruit at the pulmonary area also perceptible to a lesser extent over the praecordium. He was discharged from hospital at ten months old weighing 9 lb. and in a fair condition. No further panting attack occurred and progress was uneventful until three-and-a-half years of age, when he again attended the Out-patient Department at Great Ormond Street under Dr. D. Paterson for bilious attacks and diarrhoea. He was sent to see Sir Thomas Lewis at University College Hospital, who, in a personal

communication, reported the following : ' He seems to have little or no enlargement of the heart. The murmur is difficult to time, I make the main murmur diastolic. Stenosis of the mitral valve at this age is so rare that I hesitate very much to diagnose. I have heard no murmur like it in a child

FIG. 4.—Antero-posterior X-ray of the heart during a barium swallow showing slight compression and deviation of the oesophagus to the right by the enlarged left auricle.

before. The electrocardiographic report (see fig. 1) shows gross sinus arrhythmia and extraordinary Q waves in leads II and III.'

In July, 1938, he was again fully investigated. He had suffered from whooping cough and measles the previous year, but no evidence of rheumatism in the form of pains in the limbs. His chief complaint at this time was cough with breathlessness on running or jumping, but no cyanotic attacks. There

was nothing relevant in the family history except the father who suffered from vague rheumatic pains.

FIG. 5.—X-ray of the heart in the right oblique during a barium swallow showing compression of the oesophagus by the enlarged left auricle.

PHYSICAL SIGNS. The child was well nourished but small featured, with a sallow complexion but no visible jaundice. He was 36 lb. in weight (average

for age, 46 lb.) and had a spinal scoliosis with prominence of the right chest in front. There was no cyanosis or clubbing. The heart was enlarged to the right $1\frac{3}{4}$ inches from the mid-line ; the apex beat being visible in the fifth space three inches from the mid-line. A thrill could be felt and on auscultation a localized full diastolic with characteristic pre-systolic murmur heard. No dullness was detected in the second left intercostal space. Blood pressure 104 mm. Hg. systolic and 56 diastolic ; heart rate 82 beats a minute. There were no signs of cardiac failure or venous congestion.

INVESTIGATIONS. X-ray and screening of the heart (fig. 3, 4, 5) showed moderate enlargement of the right side and also of the left auricle detected by compression of the oesophagus in the left oblique and antero-posterior positions. Electrocardiogram (fig. 2) showed some right ventricular preponderance ; sharp P waves in leads 1 and 2, inversion of P in lead 3 ; well-marked Q waves in leads 2 and 3 ; lead 4 is normal. Dr. B. E. Schlesinger reported as follows : ' E. C. G. would fit in with congenital mitral stenosis and confirms the clinical signs and X-ray.' Blood count R.B.C. 4,020,000 per c.mm. W.B.C. 12,900. Hb. 70 per cent. Sedimentation rate 11. Van den Bergh—direct reaction negative. Indirect reaction very faint trace. Mantoux tuberculin reaction 1/1000, negative.

CONCLUSION. Taking into consideration the history and physical signs with support from the x-ray and electrocardiogram, a diagnosis of congenital mitral stenosis in this case during life appears to be fully justifiable.

Thanks are due to Dr. Donald Paterson for permission to publish this case.

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